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Figure 1

on an ordinary mattress.

Hospital X-ray, 128-pound, 28-year old female, lying on her back on an ordinary mattress supported by a bedboard. Note that the spine and bone structure sink well below the horizontal top edge of the innerspring, with accompanying muscle strain.

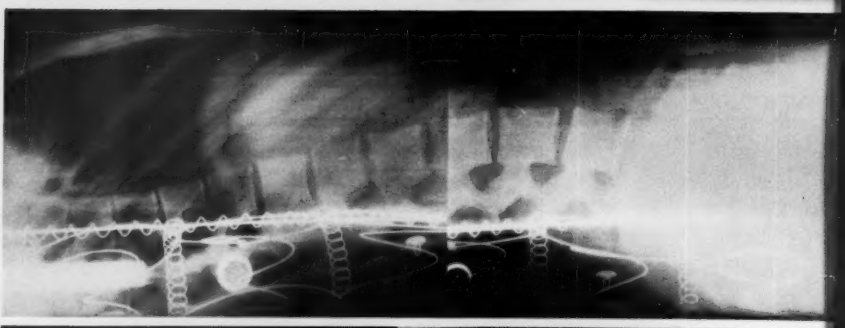

Figure 2

on Firmbak Flexiboard mattress.

Hospital X-ray, same 128-pound, 28-year old female as in Figure 1, lying on her back on the Firmbak Flexiboard mattress. Compare position of spine and bone structure with Figure 1. Support is provided by the mattress itself, permitting the muscles to rest.

Arrows indicate top of mattress.

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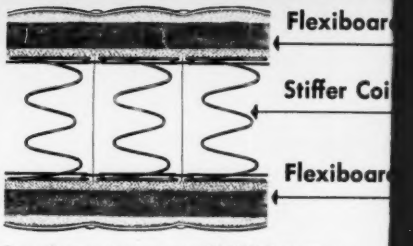

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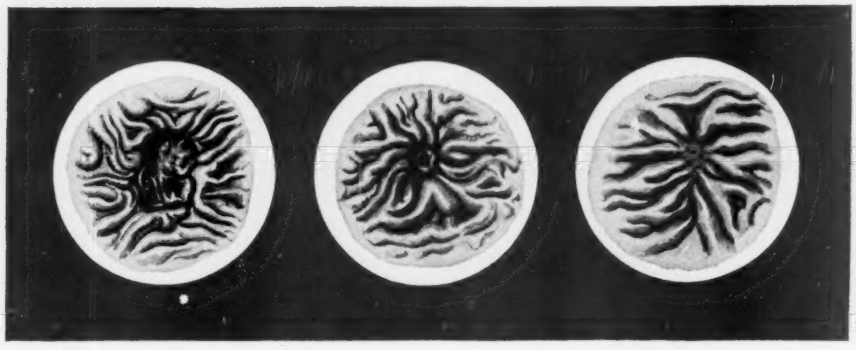

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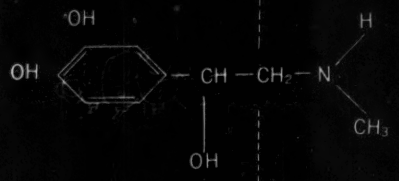
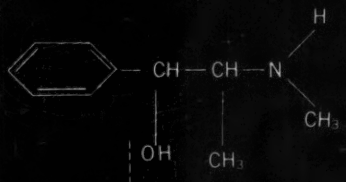
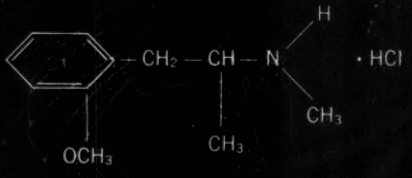




metamorphosis of a molecule



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Volume 245 AUGUST 30, 1951 Number 9

THE RECURRENCE OF VASOCONSTRICTOR ACTIVITY AFTER LIMB SYMPATHECTOMY IN RAYNAUD'S DISEASE AND ALLIED VASOMOTOR STATES*

CHARLES W. ROBERTSON, M.D.,† AND REGINALD H. SMITHWICK, M.D.‡

BOSTON

TWO types of study are commonly employed in evaluating the physiologic effectiveness of sympathetic denervation of the extremities: those methods based on the presence or absence of sweating in the area denervated and those based on the presence or absence of vasoconstrictor activity in the denervated area.

The present report deals with an evaluation of the vasoconstrictor activity in extremities after a number of different operations on the sympathetic pathways to the extremities and a comparison of these physiologic effects with the clinical results in a group of patients having intact peripheral main-vessel circulation before and after operation. The vasoconstrictor activity was evaluated by the response of estimated digit blood flow to a standard vasoconstrictor stimulus, the magnitude of the response being the basis for deciding whether or not residual or recurrent vasoconstrictor activity was present. The standard stimulus was a cool-room exposure for one hour at 68°F. carried out after a similar exposure of the patient for one hour in a warm room at 83°F. The response was quantitated by comparing the warm-room and cool-room surface temperatures at the tips of the digits after one hour in each test environment and, simultaneously, the estimated digit blood flow as shown by digit plethysmography. Patients were studied at rest, under basal conditions, and were unclothed except for a light cotton blanket over the midsection. The plethysmographic data were based on the percentage change in the cool-room pulse deflection and venous-occlusion blood flow when compared with the preceding warm-room values. We did not compare the actual values as demonstrated by plethysmography before and after operation, but only the percentage change in the cool environment before and after operation. All plethysmographic studies were carried out with the digits at approximately cardiac level.[1]

The arbitrary criteria chosen in the evaluation of vasoconstrictor activity were as follows:

On the basis of surface-temperature study: If the digit temperature fell below 80°F. after one hour in the cool room (68°F.) we designated this response vasomotor defect A. On the basis of the plethysmography data: If the cool-room study

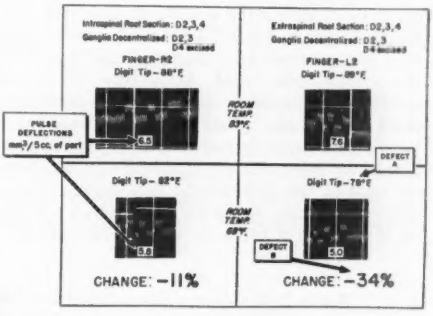

FIGURE 1. *Average Height in Millimeters of the Digit Pulse Oscillation, Representing the Indicated Pulse Deflection. The warm-room and cool-room study of the right index finger (R_2) is shown on the left, that of the left index finger (L_2) on the right.*

demonstrated a decrease of 20 per cent or more in estimated flow when compared with the warm-room study, we called this response vasomotor defect B.

The percentages in the following discussion refer to extremities studied. Figure 1 demonstrates these two "defects." In our opinion, either defect represents vasoconstrictor activity dependent on intact sympathetic pathways. The plethysomographic requirement is considerably more stringent than the surface-temperature requirement as we employ it, but these criteria were selected to give wide-range test standards for comparison of the various operative technics.

*From the Departments of Surgery, Boston University School of Medicine and the Massachusetts Memorial Hospitals.

This study was supported in part by a research grant from the National Heart Institute of the National Institutes of Health, Public Health Service.

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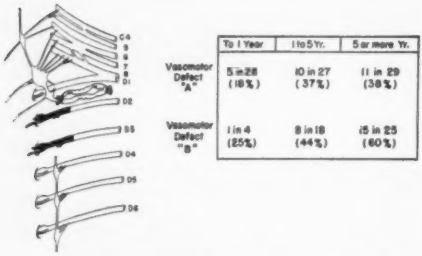
‡Professor of surgery, Boston University School of Medicine; surgeon-in-chief, Massachusetts Memorial Hospitals.

Upper-Extremity Denervation

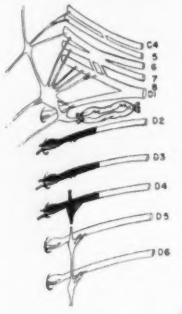
Figure 2 (Routine 1: 1940) represents the incidence of vasomotor defects A and B following the upper-extremity sympathectomy described by Smithwick in 1940.[2] In this procedure the second- and third-dorsal spinal nerves were excised as indicated by the blacked-out portions in the diagram. The attempt was made in each case to divide the nerve roots within the arachnoid (so-called "intraspinal" root section). The sympathetic ganglia were not removed but "decentralized" by dividing the sympathetic trunk below the third dorsal sympathetic ganglion, enclosing the second and third sympathetic ganglia in a silk cylinder and suturing this into the muscular layers of the wound. The latter maneuver was designed to avoid exposed cut ends of the sympathetic pathways in the hope that regeneration would be reduced to a minimum. In this group of patients, as in those operated on the two operative categories ("1940" and "1947") without regard to the various combinations of "intraspinal" and "extraspinal" root sections dictated by the surgeons.



	To 1 Year	1 to 5 Yr.	5 or more Yr.
Vasomotor Defect "A"	5 in 28 (18%)	10 in 27 (37%)	11 in 29 (38%)
Vasomotor Defect "B"	1 in 4 (25%)	8 in 18 (44%)	15 in 25 (60%)

Figure 2. *In the Above and Following Diagrams the Portions of the Nervous System Excised Are Shown in Black.*

It will be noted in Figure 2 that roughly one fifth of extremities denervated by the "1940" technic show first-year vasomotor activity, which might be interpreted as the incidence of patients showing incomplete denervation after this operation. The vasomotor defects present in the one- to five-year group and in the groups studied five years or more after operation probably represent anatomic regeneration. If it were due to a "physiologic reorganization" of the residual pathways discovered by Wrete,[3] Skoog[4] and others,[5, 6] the recurrent vasoconstrictor activity should appear less than one year after operation.



	To 1 Year	1 to 3 Years
Vasomotor Defect "A"	2 in 33 (6%)	6 in 22 (27%)
Vasomotor Defect "B"	0 in 9	8 in 19 (42%)

Figure 3.

In 1947 the operation was modified, as indicated in Figure 3. The operation was extended to include by the "1947" operation described below, whether the operator considered the operation "intraspinal" or "extraspinal" has seemed to make no significant difference in the incidence of postoperative vasomotor defects. The latter term has been applied to those operations in which the spinal-nerve root division is proximal to the posterior-root ganglion but outside the arachnoid. We have therefore placed all patients having root section in one of the fourth-dorsal spinal nerve. This is facilitated by removing a segment of the fourth rib in addition to the segment of third rib removed in the "1940" operation. The fourth-dorsal sympathetic ganglion is usually excised for microscopical study, and the sympathetic ganglia D_2 and D_3 are decentralized with a silk cylinder as before. In the subsequent three years we have noted the vasomotor defects as indicated. These data suggest that although the

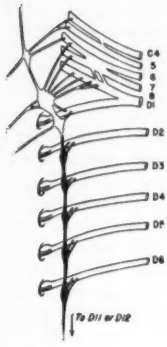
Table 1. *Correlation of Clinical and Physiologic Results. Raynaud's Disease and Allied Vasomotor States.**

	Upper-Extremity Denervations (Root Section, "1940" and "1947" Operations)								
	Vasomotor defects A and B absent (complete denervation)				Vasomotor defects A or B present (incomplete denervation)				Total extremities studied
Time after operation	*No. of Extremities*	*Results*			*No. of Extremities*	*Results*			
		good	*fair*	*poor*		*good*	*fair*	*poor*	
Less than 1 yr.	53	31	22	0	14	1	10	3	67
1-5 yr.	20	9	10	1	35	4	23	8	55
5-15 yr.	6	3	3	0	25	11	10	4	31

*All peripheral pulses present before operation.

first-year results have been improved not a great deal has been added concerning the one- to three-year studies.

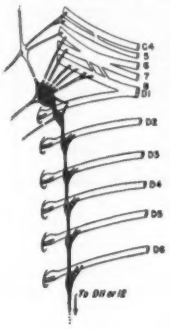
In attempting to evaluate the vasomotor activity in the upper extremities after removal of long segments of the *sympathetic chain alone* we have utilized a group of patients on whom we have carried out subtotal or total thoracic sympathetcomy for hypertension. These patients, with rare exceptions, had no peripheral-vascular symptoms or manifestations. In the group designated as "transthoracic 1" (Figure 4), the thoracic chain has been removed from D_2 through D_6 or more, — the majority through D_{11} or D_{12} inclusive. First-year or residual activity is present in 20 per cent of extremities and a high proportion of vasomotor defects (31 to 62 per cent).



	To 1 Year	1 to 5 Years
Vasomotor Defect "A"	7 in 42 (17%)	14 in 26 (54%)
Vasomotor Defect "B"	1 in 3	14 in 16 (88%)

FIGURE 4.

On the basis of this evaluation of upper-extremity denervation one can say that extremities operated on by technics that involve either root section or removal of long segments of the sympathetic chain alone, including the stellate ganglion, demonstrate less than 20 per cent residual vasomotor activity in the first-year studies. The late physiologic results of root section seem to be somewhat better than those of extensive ganglionectomy alone. (Without material it is not possible to compare the two technics clinically.) The hopeful aspect of this situation is that in our experience over 85 per cent of patients operated on for Raynaud's disease and allied vasomotor states of the upper extremity by the one- to five- year follow-up shows a recurrent vasomotor-activity percentage of formidable proportions (54 to 88 per cent).



	To 1 Year	1 to 5 Years
Vasomotor Defect "A"	1 in 53 (2%)	17 in 54 (31%)
Vasomotor Defect "B"	0 in 3	20 in 32 (62%)

FIGURE 5.

If the stellate and the first dorsal ganglion are removed in addition to long segments of the thoracic chain as in the group designated as "transthoracic II" (Figure 5), the first-year activity percentage is very low (2 per cent) in the group studied. However, the one- to five-year follow-up studies show the "1940" technic have considered the operation worth while and might be classified as "good" or "fair" clinical results five years or more after operation (see Table 1). Even though vasomotor manifestations may be present, these are much less disabling, and in the vast majority of cases patients are able to work. At the present time we employ the "1947" operation, reserving the removal of the stellate for a later operation if this should become

TABLE 1 (*Concluded*).

	Lower-Extremity Denervations (L_1, L_2 and L_3 or L_3 and L_4)								
	A and B absent (complete denervation)				A or B present (incomplete denervation)				
Time after Operation	*No. of Extremities*	*Results*			*No. of Extremities*	*Results*			
		good	*fair*	*poor*		*good*	*fair*	*poor*	
Less than 1 yr.	34	22	12	0	5	4	1	0	39
1-5 yr.	12	10	2	0	6	3	3	0	18
5-15 yr.	10	10	0	0	3	3	0	0	13

necessary. The latter procedure is best carried out through an anterior approach.

Lower-Extremity Denervation

Lumbar sympathectomy, as usually carried out, includes L_1, L_2 and L_3, or L_2 and L_3. These operations are associated with a somewhat lower incidence of vasomotor activity by these standards; nevertheless, the defects do occur, as indicated in Figure 6. Clinically, in the study group, all lower-extremity sympathectomies have been classified as "good" or "fair" five years or more after the operation (see Table 1).

	To 1 Year	1 to 5 Years	5 or more Yr.
Vasomotor Defect "A"	3 in 51 (6%)	2 in 18 (11%)	3 in 15 (20%)
Vasomotor Defect "B"	2 in 24 (8%)	2 in 11 (18%)	3 in 13 (23%)

Figure 6.

Correlation of Vasomotor Defects with Clinical Evaluation in Raynaud's Disease and Allied Vasomotor States

A correlation of clinical and physiologic results was possible in most of the cases studied. A "good" clinical result was claimed only if the patient was enthusiastic about the result and considered himself "cured" or "75 per cent or more improved." A "fair" clinical result was recorded if the patient definitely considered the operation "worth while" or "satisfactory" and would undergo surgery again in the light of the past surgical experience but in whom the disorder was not completely relieved. This category included patients who had successful local amputations or who demonstrated no progression of the disorder. A "poor" clinical result was recorded if the patient was dissatisfied with the operation for any reason and would *not* agree to submit to operation again in the light of the past surgical experience. Progression of symptoms and disease was present in the majority of this group.

In making this comparison between the physiologic effects of operation and the clinical evaluation, we have selected only patients in whom all peripheral main-vessel pulsations were present before and after operation, so that the factor of poor arterial inflow on an organic basis could be minimized in judging the effects of operation on the peripheral blood flow. In this way, we have attempted to ascertain the "calculated risk" of vasoconstrictor activity after extremity sympathectomy, which depends on the inherent limitations of the various operations employed.

It will be noted that we did not find the close correlation between physiologic evidence of recurrent vasoconstrictor activity and clinical results that was recently reported by Felder, Simeone, Linton and Welch.[7] Table 1 summarizes the correlation of clinical results and the presence or absence of the described vasomotor defects A and B in upper extremities operated on by both "1940" and "1947" technics of root section and in lower extremities operated on by removal of lumbar sympathetic ganglia 1, 2 and 3 or 2 and 3.

Summary

To evaluate the effectiveness of sympathetic denervation of the extremities in elimination of the vasoconstrictor mechanism, clinical and laboratory examinations have been carried out on several groups of patients whose extremities have been denervated by a variety of standard technics. The cases have been further subdivided according to duration of follow-up, and the clinical results are related to the completeness or incompleteness of sympathetic denervation in each time category. With regard to the upper extremity, either root section or ganglionectomy will eliminate the vasoconstrictor activity in over 80 per cent of extremities studied up to one year after operation. However, up to 65 per cent of such extremities, depending on the criteria employed, will show evidence of incomplete denervation if studied one to five years after operation — and up to 80 per cent will show such evidence if studied five years or more after operation. In contrast to this, we have found that over 85 per cent of upper extremities denervated by root section for vasomotor disorders can be classified as "good" or "fair" clinically five to fifteen years after operation.

With regard to the lower extremities studied, over 85 per cent of the vasomotor group demonstrated complete denervation up to one year after operations of the standard type if main-vessel circulation was intact before and after operation. Up to one third of lower extremities in this vasomotor group demonstrated evidence of incomplete denervation in the one- to five- and five- to fifteen-year follow-up study. Clinically, all the lower extremities in this group were classified as "good" or "fair."

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CALCIFICATION OF THE VAS DEFERENS*

Its Relation to Diabetes Mellitus and Arteriosclerosis

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IN 1942 Marks and Ham[1] reported 9 cases of calcification of the vas deferens demonstrated by roentgenography in patients seen at the New England Deaconess Hospital. Since then an increasing number of patients in the practice of Dr. Elliott P. Joslin and his associates have been found with this rather unusual condition. It is, however, not a newly discovered condition, for calcium deposits within structures of the male genital tract have been recognized and reported at intervals for more than a century. All previously reported cases involving calcification in either the seminal vesicles or the vas deferens have been summarized in Table 1.

The first article in the American literature on this subject appeared in 1906 when George[9] reported 2 cases, one with calcium deposition in the right seminal vesicle and the other with calcification of the left vas deferens. It is our opinion that calcification within these two structures is the result of different processes and that the conditions are not etiologically similar. We are concerned in this report only with cases of vas-deferens calcification. Bianchini,[16] in 1930, first reported calcification that was confined to the vasa deferentia and their ampullae and had been observed ante mortem by x-ray.

The first case to be documented in the American literature after diagnosis by roentgenography in a living patient was the initial case seen in this hospital in 1939 and reported previously.[1] Six of the 9 cases reviewed in this earlier article occurred in patients with diabetes, a relation not noted in the literature on the subject prior to that time. O'Connor[21] and Andersen[22] have since added reports of single cases.

It is the purpose of this publication to present data concerning the 60 patients seen by us who have been found by roentgenography to have calcification within the walls of the vas deferens. Seven of these cases were among those listed in the previous report.[1]

TABLE 1. *Previously Reported Cases of Calcification Within the Male Genital Tract.*

CASE NO.	YEAR	AUTHOR	LOCATION OF CALCIFICATION	AGE OF PATIENT	MEANS OF DIAGNOSIS
1	1830	Clement[3]	Both seminal vesicles	—	Autopsy
2	1836	Lallemand[3]	Both seminal vesicles	—	Autopsy
3	1855	Dupley[4]	Both ampullae	80	Autopsy
4	1855	Dupley[4]	Both ampullae	81	Autopsy
5	1861	Rokitansky[5]	Both seminal vesicles	—	Autopsy
6	1876	Kleb[6]	Both seminal vesicles	—	Autopsy
7	1893	Orth[7]	Both vas deferens	—	Autopsy
8	1903	Chiari[8]	Both ampullae and both seminal vesicles	68	Autopsy
9	1903	Chiari[8]	Both ampullae	56	Autopsy
10	1903	Chiari[8]	Both ampullae	75	Autopsy
11	1906	George[9]	Right seminal vesicle	63	Autopsy
12	1906	George[9]	Left vas deferens	53	Autopsy
13	1909	Simmonds[10]	Both vasa deferentia	60	Autopsy
14	1909	Simmonds[10]	Both vasa deferentia	54	Autopsy
15	1909	Fraenkel[11]	Both vasa deferentia	45	Autopsy
16	1909	Fraenkel[11]	Right vas deferens	62	Autopsy
17	1913	Chetwood[12]	Both seminal vesicles	—	Operation
18	1922	Kretschmer[13]	Left seminal vesicle	14	X-ray examination
19	1929	Dopheide[14]	Both ampullae	80	Autopsy
20	1929	Dopheide[14]	Both ampullae	77	Autopsy
21	1929	Cotteno[15]	Both seminal vesicles	62	X-ray examination
22	1930	Bianchini[16]	Both vasa deferentia and both ampullae	34	X-ray examination
23	1930	Schellenberg[17]	Both vasa deferentia and both ampullae	48	Autopsy
24	1932	Hofer[18]	Both ampullae	61	X-ray examination
25	1935	Janker[19]	Both seminal vesicles	59	X-ray examination
26	1935	Janker[19]	Left ampulla	57	X-ray examination
27	1935	Janker[19]	Left ampulla	43	X-ray examination
28	1935	Janker[19]	Left vas deferens	26	X-ray examination
29–37	1942	Marks and Ham[1]	Vas deferens (9 cases)	30 to 79 (average, 51.8)	X-ray examination
38	1942	Lowsley[20]	Both ampullae	67	X-ray examination
39	1947	O'Connor[21]	Both vasa deferentia	73	X-ray examination
40	1950	Andersen[22]	Both vasa deferentia	62	X-ray examination

ANALYSIS OF CASES

The average age of the entire group of 60 patients at the time of demonstration of calcified vas deferens was fifty years. Fifty-six of these patients had dia-

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betes mellitus, which had been acquired at an average age of 33.4 years. Calcification was first noted within the vas deferens by x-ray after an average duration of 18.3 years of diabetes. The two youngest patients in the group were twenty-nine years of age. Each had had diabetes for seventeen years; one had roentgen evidence of slight arterial calcification and the other had none; the latter died within the same year of coronary occlusion.

FIGURE 1. *Calcification of the Vasa Deferentia: the Only One Yet Seen with Both Ducts Calcified in Their Entire Length (Patient Aged Forty-Four, with Diabetes for Five Years). (Reproduced from Marks and Ham[1] by Permission of the Publisher.)*

Of 33 patients whose age at onset of diabetes was less than forty years, the average duration of the disease was twenty-two years before calcification of the vas deferens was demonstrated. In the 23 cases with onset of diabetes after the age of forty, the calcification of the vas deferens was demonstrated after an average of only thirteen years of diabetes. Of the 14 patients in whom diabetes had been present *less* than fifteen years before calcification was noted in the vas deferens, 12 had had onset of their diabetes after the age of forty. Conversely, among those 42 patients with diabetes of *more* than fifteen years' duration before calcified vasa deferentia were noted, onset of diabetes had occurred before the age of forty in 31 of the 42 cases. In general, then, the vasa deferentia may calcify after a relatively short duration of diabetes when the disease begins after the age of forty, whereas with patients acquiring diabetes prior to the age of forty the disease has usually been present for at least fifteen years before calcification is noted in the vas deferens. In only 2 of the 60 cases did it appear that an acute or chronic infectious disease played any etiologic role. These 2 patients, 1 of whom was not diabetic, gave histories of severe neisserian infections. In all the other patients the condition was attributed to degenerative changes within the wall of the vas deferens, similar to those seen in a medium-sized artery that has undergone arteriosclerotic changes.

Review of the marital and dependency status of the patients in this group shows 9 men to have been unmarried, whereas 2 were divorced and 3 others had been married 2 or more times. The remaining 46 patients of the series had been married

FIGURE 2. *Calcification of Portions of Vasa Deferentia Medial to Ureters; Arterial Calcification also Present (Patient Aged Forty-Nine, with Diabetes for Twenty-Five Years).*

only once; of these 39 have had children. There was no known instance of pregnancy occurring after calcification was noted within the vas deferens of the husband. However, it is noteworthy that in the series there were only 3 married men who were less than forty years of age at the time of demonstration of calcified vas deferens.

Analysis of the racial distribution of the diabetic patients in this series shows it to be similar to that seen in the over-all group of diabetic patients of this region. There were 12 Jewish patients, 3 Italians and 1 patient each from India and South Africa.

Twenty-seven of the 56 patients with diabetes revealed an associated family history of diabetes.

Many complications attributable to diabetes were present in the patients comprising this group. Arterial calcification was present in 53 of the 60 cases and was found to be moderate or severe in 33 cases; in 20 cases only minimal involvement was seen. Thirty-seven patients had retinitis in varying degrees of severity. Proteinuria was present in 27 patients, of whom 24 also showed elevation of the blood pressure to hypertensive levels (above 140/90). In 13 patients the clinical symptomatology of diabetic nephropathy[23] was apparent.

Forty-five of the patients in this series are still living. Among the 15 who have died, 7 deaths were attributed to arteriosclerosis; 6 of these had fatal coronary occlusions. Four patients died of carcinoma. In 2 cases nephritis was the cause of death. The remaining 2 deaths were reportedly due to infection and diabetes. The average age at death among the 15 patients, 2 of whom were not diabetic, was 59.4 years.

Although no prognostic significance can be assumed, it is of interest that of the 15 patients who have died 8 were found to have calcified vas deferens within a year of their death. The average duration of life for patients after calcification was first noted in the walls of the vas deferens was 2.3 years. Certainly in several instances calcium deposits had undoubtedly been present for some time before evidence of it was observed. In the majority of cases there is no way of knowing how much time elapsed between actual onset and demonstration of the calcification. Six patients who have been closely followed during recent years showed no evidence of calcification in any part of the generative tract on earlier films of good quality but on subsequent films showed beginning calcification in the ampullary portions of the vasa deferentia. The process has slowly progressed during observation periods of three to seven years and has been paralleled by slow progress of arterial calcification during the same period.

Of the 60 cases studied the scrotum, or at least its major portion, was shown on the films of 39 patients. In only 8 of these 39 cases was there evidence of calcification in the extrapelvic portion of the vasa. It is of further interest to note that

FIGURE 3. *X-Ray Films Taken after Injection of Hypogastric Artery.*
Note course of internal pudendal artery.

FIGURE 4. *X-Ray Film Taken after Injection of Testicular Artery.*
The course below the inguinal ring is similar to that of the vas deferens.

in the 52 cases in which the calcification was seen only in the intrapelvic portions this calcification was evident only in the portions of the vasa that are medial to the ureters. There thus appears to be some delay in appearance of the calcification in that portion of the vas that lies between the ureter and the inguinal canal. We do not know the cause for this variation of incidence of calcification in the several segments of the vas, but it is of interest to note that the wall of the duct is very much thinner in its ampullary portion.

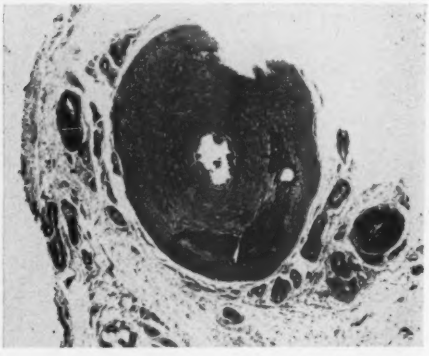

FIGURE 5. *Photomicrograph Showing Calcification within Muscular Wall of Vas Deferens.*

The calcification was bilaterally symmetrical in extent in all but 11 cases; in all but 3 additional cases it was equal in degree of density.

DISCUSSION

We lack the necessary evidence for proving the etiology or pathogenesis of this process, but we believe that a more discriminative awareness on the part of roentgenologists and clinicians who examine or treat diabetic patients would result in more frequent recognition of the condition. The finding of a linear calcification in the pelvis of a diabetic male should arouse the observer's interest and incite him to trace its course to determine whether the calcification is within the vascular system or the genital tract. The anatomic location and course of the intrapelvic portion of the vas deferens differ from that of any artery in the male pelvis, thereby facilitating recognition of this portion of the duct. In addition, the condition should be suspected when, on films of the pelvis or abdomen, parallel lines of density resembling a calcified artery are seen to pass obliquely downward and medially across the shadow of the obturator foramen. The internal pudendal and testicular arteries are also projected in the obturator foramen and may be calcified. They are of about the same caliber as the vas but can be distinguished from it if sufficiently long segments are calcified. The internal pudendal artery arises from the hypogastric artery and curves medially below the obturator foramen to supply the tissues around the anus. The testicular artery parallels the vas below the inguinal ring but can be differentiated if its site of origin in the aorta can be identified. Roentgenograms of injected specimens illustrate the points of similarity and difference.

The occurrence of the majority of cases of calcified vas deferens in patients with diabetes mellitus is of considerable interest. A conservative estimate of the number of nondiabetic patients examined in our department of roentgenology during the period in which these cases were discovered would approximate 6 times the number of diabetic patients examined. Thus, the hospital and ambulant patient group among which these cases were discovered was predominantly nondiabetic. Can this be considered a specific complication of diabetes, and is it explainable simply on the basis of the increased predisposition to early degenerative changes in the vascular systems of diabetics? If so, then it must be assumed that this is due to a structural rather than a functional relation between the vas deferens and the blood vessels. If this condition represents sclerotic changes as commonly seen in the blood vessels, why is there not a much higher incidence among nondiabetic patients of the older age groups? Should not one expect to see also an increased incidence among patients with hypercholesterolemia, in which cases early generalized arteriosclerotic changes are frequent?

Some observers[8, 9] believed that two forms of pathologic involvement may be seen in these cases. In the so-called noninflammatory form the lumen of the duct remains widely patent; the calcified deposits are found within the muscular elements that comprise the wall of the duct as shown in Figure 5. After a chronic tuberculous, neisserian or other urogenital-tract infection, the inflammatory form of change is most commonly seen; in this there may be thrombosis with partial or complete occlusion of the lumen of the vas deferens, with rupture through the intimal mucosa.

SUMMARY

Sixty cases of calcification within the walls of the vas deferens are reported. This unusual condition was associated with diabetes mellitus in 56 cases. The relation of this process to diabetes, particularly to the vascular degenerative complication of diabetes, is discussed.

It is our opinion that calcification within the vas deferens represents a relatively specific degenerative complication of diabetes.

All previously reported cases of calcification within the male genital tract have been tabulated.

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CLINICAL APPRAISAL OF HEXAMETHONIUM (C6) IN PERIPHERAL VASCULAR DISEASES*

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SINCE Paton and Zaimis[1] suggested the clinical potentialities and demonstrated the ganglion-blocking properties of pentamethonium (C5) and hexamethonium (C6), much interest has centered on these compounds. Studies by Arnold and his co-workers,[2] using C5, and by Burt and Graham, using C5 and C6,[3] demonstrated that these agents are 5 times as potent as tetraethylammonium (TEA). Pentamethonium iodide in doses of 50 mg. given intravenously produced a rise of digital skin temperature with a simultaneous increase in digital blood flow and pulse volume lasting for one to two hours. Studies in this laboratory[4] confirmed the observations of these British investigators and showed that the increase in skin temperature of the toes after 50 mg. of C6 ion (96 mg. of hexamethonium dibromide§) exceeded that produced by the intravenous administration of 50 mg. of Priscoline and 400 mg. of TEA. In addition doses of 50 to 100 mg. resulted in increases of foot blood flow that were not significantly different from those following epidural or intrathecal lumbar block.[5]

These observations are in contrast to those of Grob and Harvey,[6] who found that C5 produced a greater increase in skin temperature than 400 mg. of TEA but was less effective than lumbar block. This discrepancy might be due to the fact that these workers used C5 instead of C6 but more likely is due to differences in dosage. These workers employed average doses of only 20 mg. of pentamethonium diiodide (8 mg. of C5 ion) or dibromide (10 mg. of C5 ion), whereas in our studies 50 to 100 mg. of C6 ion was necessary to achieve maximum foot blood flows.[5]

Because of the marked ganglion-blocking action of C6 it seemed pertinent to investigate clinically the effects of the drug in the management of patients with various types of peripheral vascular disease.

Methods and Results

In the present series there were 29 patients with vascular disease of the extremities. These included 2 patients with arterial embolism, 1 with primary arterial thrombosis, 3 with Buerger's disease, 2 with Raynaud's phenomenon, 1 with causalgia, 5 with arteriosclerosis obliterans and 16 with thrombophlebitis. All these patients were hospitalized during their course of treatment with C6.

Case Reports

CASE 1. The first patient was a 28-year-old man with rheumatic heart disease and acute bacterial endocarditis. On the twelfth hospital day he developed an arterial embolism to the right leg below the knee, manifested by a cool foot and weakened dorsalis-pedis and absent posterior-tibial pulsations on that side. In addition, there was marked tenderness of the right calf and a positive Homans sign, suggesting the presence of secondary thrombophlebitis. A paravertebral block on the right was performed, resulting in partial relief of pain and increased dorsalis-pedis pulsations persist-

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§Supplied by Dr. H. Sidney Newcomer, of E. R. Squibb and Sons, New York City.

ing for 3 hours. Priscoline administered by mouth in doses of 50 mg. produced no improvement.

TEA in a dose of 450 mg. given intravenously resulted in partial relief of pain and a fleeting return of pulsations in the posterior tibial artery lasting for one-half hour. Fifty mg. of C6 ion given intravenously relieved the pain in the right leg for six hours. The patient was able to extend the leg, and there was decreased tenderness to palpation. The posterior-tibial pulsation increased to normal, and the temperature of the leg and foot rose to equal that of the opposite extremity. The effects reached a maximum one-half to one hour after injection and then gradually waned over a period of seven hours, after which time the patient demanded another injection because of return of pain. By means of repeated doses at eight-hour intervals he was maintained in a relatively pain-free state. This regimen was continued for 5 days, with complete relief of both objective signs and pain. The only toxic effect was occasional blurring of vision occurring 5 to 10 minutes after the injection. Five weeks after C6 was discontinued the patient developed a popliteal aneurysm on the right and died three weeks later.

Case 2. A 50-year-old man developed an embolus to the right leg 3 weeks after an acute myocardial infarction. This was followed by extreme pain in the leg, which was cold and pale below the middle third. The toes were pale blue in color. No pulsations were felt below the femoral artery. The pain was relieved for four hours after lumbar paravertebral block, but the patient refused the manipulation necessary for daily treatments.

At this point treatment with C6 was attempted, the foot of the bed first being elevated on 6-inch blocks. The blood pressure before treatment was 100/70 mm. Hexamethonium was slowly given intravenously at a rate of 1 mg. of the ion per minute while the blood pressure was recorded continuously in the opposite arm. After 15 mg. of the drug had been given the blood pressure fell to 78/52 mm. but stabilized at 84/64. The patient did not experience angina or faintness at this level of blood pressure. There was no immediate color change. However, when the involved extremity was hung over the side of the bed with the foot resting on a chair, there was slow but definite improvement in the color of the leg and a simultaneous rise in skin temperature. Although the pulsations did not reappear the patient noted some return of sensation in the foot.

Treatment was continued for 3 weeks, — 20 mg. of C6 given intramuscularly twice daily, with the same positioning of the body, that is, with the foot of the bed elevated and the involved extremity hanging over the side for 3 hours after each injection. There was no angina and no change in the electrocardiogram. At the end of this period the patient still complained of numbness and pain in the foot at night. By this time his general condition had improved sufficiently to permit surgical intervention. A right-lumbar sympathectomy was performed, with considerable improvement in night pain and in the color of the foot but still without return of pulsations. He improved sufficiently to walk with the aid of a cane and has been discharged from the hospital.

Case 3. A 43-year-old man was admitted to the surgical service with painful gangrene of the right foot of 3 days' duration. There was no history of claudication, diabetes or vascular diseases. The right leg was cold below the knee. There was purplish-black discoloration over the distal half of the foot and erythema of the lower quarter of the leg. No pulses were palpable below the femoral artery on the involved side. The pulses in the left foot were easily felt, and the remainder of the vascular examination was within normal limits. Because of intense, constant pain the patient received 2 lumbar paravertebral blocks, which resulted in moderate relief of pain for 3 to 4 hours, but there was little change in the temperature of the leg. Fifty mg. of C6 ion was then given intravenously every 6 hours, resulting in marked subjective relief of pain for 5 to 6 hours. In addition there was warming of the leg as far distally as the ankle.

Treatment with C6 was continued for 7 days, during which time the absence of pain and warmth of the leg were maintained. Because of this improvement it was decided to attempt amputation below the knee instead of a mid-thigh amputation as originally contemplated. After the operation, 50 mg. of C6 was given every eight hours for 3 days and then every 12 hours for 7 days. There was uneventful healing of the stump. Six weeks after operation a prosthesis was fitted and the patient was discharged from the hospital.

Pathological examination of the amputated leg confirmed the diagnosis of primary thrombosis, as there was no evidence of pre-existing arteriosclerosis obliterans or of Buerger's disease. In the opinion of the surgical service C6 performed two useful functions: It maintained the patient in a pain-free state and by improving the nutrition of the leg prior to operation and maintaining it after operation it insured good healing of the stump, thus permitting amputation below the knee.

Case 4. A 47-year-old man had a history of intermittent claudication of 4 months' duration and gangrene of the left first toe for 2 weeks. Forty mg. of C6 ion given intravenously resulted in almost immediate relief of pain and return of normal color to the toes 15 minutes later. There was marked postural hypotension but no other side-effects. After administration of C6 the patient experienced his first comfortable night in several months. On the following evening he was given 100 mg. of Demerol, which was less effective than C6 in relieving the pain. A left-lumbar sympathectomy was performed, with good results.

(Two other patients with Buerger's disease also experienced relief of pain after injection of C6 and later underwent sympathectomy with subsequent improvement.)

Case 5. This patient was a 34-year-old man with Raynaud's phenomenon secondary to frostbite. He complained of pallor and numbness of the fingers precipitated by cold but not by emotion. At the age of eight years his hands and feet had been frostbitten, and three years ago the terminal 2 digits of the middle finger of the left hand were amputated because of gangrene. There were trophic changes of the index fingers of both hands. Fifty mg. of C6 ion given intramuscularly blocked the phasic color changes produced by cold for as long as twelve hours. The patient was discharged from the hospital on a dosage of 50 mg. of C6 administered subcutaneously two hours before arising in the morning. With this treatment he experienced no pain of the hands and feet on exposure to cold during his working day. He was then given hexamethonium dibromide orally in single daily doses. An oral dose of 1.5 gm. of hexamethonium dibromide (830 mg. of C6 ion) resulted in relief of his symptoms comparable to that caused by the subcutaneous dose of 50 mg. of C6 ion. Lesser doses given by mouth were ineffective. Thus the active oral dose was approximately 17 times greater than the active parenteral dose.

In another patient with Raynaud's phenomenon, characteristic color changes developed when the fingers were placed in cold water. This cold-induced attack was completely blocked for 6 hours by 50 mg. of hexamethonium ion.

Case 6. A patient with causalgia of the right hand following an old injury was given 50 mg. of C6 intravenously, with complete relief of pain and hyperesthesia for several hours. An injection of sterile saline solution on the following day was without benefit. Cervical sympathectomy was performed subsequently, with permanent relief of pain.

Case 7. A 43-year-old man with diabetes mellitus had complained of intermittent claudication for 2 years. Pain in the calves developed after walking one-half block during the month preceding admission to the hospital. No pulses were palpable below the femoral artery on the right. Fifty mg. of C6 ion were administered intramuscularly every 6 hours for 2 days, at the end of which time the patient was able to walk a distance equivalent to 20 city blocks before claudication appeared. The marked increase in exercise tolerance remained during an additional week of treatment. However, severe postural hypotension forced the patient to remain in bed for several hours after each injection of C6, so continued treatment was not considered practical. A lumbar sympathectomy was performed with good results.

Four other patients also experienced marked prolongation of onset of claudication after administration of C6 and later had relief of pain after sympathectomy.

Case 8. A 28-year-old woman in the fourth month of pregnancy entered the hospital complaining of a painful swelling of the left leg of one day's duration. Physical examination revealed a positive Homans sign and calf tender-

ness extending into the popliteal region. Lumbar sympathetic block resulted in relief of pain for 3 hours. The intravenous injection of 50 mg. of C6 ion was followed in 15 minutes by complete relief of pain and tenderness for six hours. When this dose was repeated at 6-hour intervals the pain did not return. After 48 hours of therapy mild calf tenderness on walking was the only remaining symptom. On the third and fourth days only 2 daily injections of C6 were needed to maintain the pain-free state. On the fifth day the patient was asymptomatic, walking without a limp, and needed no further medication.

Case 9. A 24-year-old man entered with thrombophlebitis of the right leg of 3 days' duration. Five minutes after intravenous injection of 50 mg. of C6 ion, the foot became warm, pain and tenderness disappeared and the Homans sign became negative. The patient was given 50 mg. of C6 every 6 hours for 48 hours with complete and lasting relief of signs and symptoms. Heparin and Dicumarol were included in the treatment.

Similar results were obtained in 2 other cases, with intravenous administration of C6. In the remaining 12 cases, after determining sensitivity to the hypotensive action of C6 by the method given below, orders were written for 50 mg. of C6 ion to be given intramuscularly every 6 hours for the first 2 days, reducing the frequency to twice daily for the last 2 days. Instructions were given the patient to remain supine in bed (without pillows and with the bed rolled down completely) for 2 hours after each injection in order to prevent extreme hypotension. Heparin or Dicumarol, or both, were used in the accepted dosages when indicated.

A total of 16 cases of thrombophlebitis were treated. The involvement was in the lower extremities in all cases. Hexamethonium was administered intravenously in the first few cases and intramuscularly in the remainder. Dramatic and almost immediate relief of pain and tenderness was seen in all cases, every patient but one being able to walk without discomfort by the fifth day. The single exception required 2 further days of treatment to become free of symptoms.

Discussion

Schnaper, Johnson and Freis[6] demonstrated that the increase in foot blood flow after administration of 50 to 100 mg. of C6 ion in normal subjects was not significantly different from that attained after epidural or intrathecal lumbar anesthesia. Hoobler and his co-workers[7] demonstrated that the increase in foot blood flow after TEA, Priscoline, alcohol or body warming was usually less than half that following lumbar paravertebral block. Thus it seems apparent that hexamethonium has considerably greater potency than previously known peripheral vasodilator agents.

The results reported in this paper suggest that hexamethonium is as effective as paravertebral block in patients with peripheral vascular diseases. The advantage of C6 is that it may be given by hypodermic injection by the nursing staff around the clock to produce a more or less continuous increase of peripheral blood flow for prolonged periods of time. The disadvantage is the occurrence of hypotension, — particularly postural hypotension. However, with frequent doses given over long periods the postural hypotension becomes less prominent.[5] In addition, although it was available to us only in small amounts at the time of this study, C6 in large doses appeared to be effective when given orally. One hour after a single oral dose of 1 gm. of C6 ion in a normal subject exposed continuously to an environmental temperature of 68°F., the skin temperature of the toes rose to equal the umbilical temperature and remained at this high level for more than eight hours.[9] Thus the possibility of producing a prolonged "medical sympathectomy" in patients with peripheral vascular disease deserves further investigation.

Because of the marked hypotensive effects of C6, particularly after the initial dose, it is possible that dangerous collapse may be precipitated by injudicious administration of the drug. For this reason it is advisable in beginning treatment in all elderly, hypertensive or debilitated patients (who may be unusually susceptible to the hypotensive action of the drug) to determine the effect of C6 on the blood pressure prior to administering full blocking doses. This preliminary testing is accomplished by injecting the drug at a rate of 1 mg. of the ion per minute intravenously with repeated determinations of the blood pressure in the opposite arm. The rate of injection may be increased slightly after 10 mg. has been given. The injection should be halted immediately if there is any marked fall in blood pressure. This reaction may be treated by elevating the foot of the bed on 6- or 8-inch blocks, elevating and passively exercising the lower extremities and administering vasoconstrictor agents such as phenylephrine hydrochloride (Neosynephrine), 2 to 4 mg. intravenously. Epinephrine should not be used.[10] Severe collapse reactions of this type have been much more common in hypertensive patients[8] than in those with peripheral vascular disease. Furthermore, because of postural hypotension the patient must remain supine in bed for two to three hours after each injection.

The acute, severe hypotensive reactions characteristically occur only after the initial injection of C6. With subsequent administration of the drug the hypotensive effect is less marked. In patients with coronary artery disease, the hypotension and compensatory tachycardia following administration of C6 may precipitate a bout of angina.[4] It has also been reported that patients under anesthesia frequently develop extreme hypotension after this treatment.[11] This reaction may be due to blood loss associated with operative procedures rather than to the anesthesia.[12] The only other undesirable effect is the development of constipation, which can usually be managed with enemas and cathartics. Occasionally a condition resembling paralytic ileus develops, with distention, nausea and abdominal cramps. Preliminary evidence suggests that the constipation and ileus can be controlled by administering a parasympathomimetic agent such as urethane B-methylcholine chloride (Urocholine), 5 to 15 mg. orally twice or three times per day,[3] in addition to laxatives.

C6 may be of value not only in the treatment of acute types of peripheral vascular disease but in the selection of cases for sympathectomy. In the present series all patients who responded well

to C6 also exhibited a good result after sympathectomy. The converse, however, does not follow, — that patients who do not respond to C6 will not be benefited by sympathectomy, — as in many cases good surgical results have followed poor responses to lumbar block.[13, 14]

The availability of an agent producing more or less complete autonomic blockade for long periods of time suggests a trial of C6 in a wide variety of conditions, including such diverse diseases as causalgia, Parkinsonian tremor, anterior poliomyelitis and chronic ulcerative colitis, as well as other diarrheal diseases and pancreatitis. Final evaluation of hexamethonium in the treatment of such conditions as well as in peripheral vascular diseases must await long-term studies in large series of patients.

Summary and Conclusions

In a small series of patients suffering from a variety of peripheral vascular diseases, including arterial thrombosis and embolism, acute thrombophlebitis, Raynaud's phenomenon, Buerger's disease and arteriosclerosis obliterans, C6 appeared to be approximately as effective as paravertebral sympathetic block. The advantages of C6 were its ease of administration and extreme potency, permitting more or less continuous inhibition of neurogenic vasospasm for long periods. Its disadvantages were the development of hypotension, — especially in the erect position, — and constipation in a few cases.

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STEATORRHEA FOLLOWING THE USE OF ANTIBIOTICS*

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IN THE last two years several new antibiotics have become available. Three of these, — aureomycin, chloramphenicol and terramycin, — affect a wide range of bacteria and, since they are effective orally and are reputed to be without serious toxicity, have been widely used. It is generally known, however, that they may produce black tongue, vaginitis, pruritus ani and proctitis. More recently Woods and his co-workers[1] contributed greatly by pointing out the occurrence of prolonged diarrhea and pulmonary disease following the use of antibiotics. They attributed this to an overgrowth of monilia secondary to destruction of competing bacteria, causing an inflammatory response in the bowel, and chronic inflammatory lesions in the lungs.

The cases presented here of prolonged diarrhea following the use of antibiotics present a clear-cut clinical picture, further delineating this syndrome and strongly suggesting a different causative mechanism.

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Case Reports

Case 1. A 35-year-old man was subject to recurrent attacks of maxillary sinusitis. For a particularly severe attack with considerable pain he took 8 gm. of chloramphenicol (2 gm. daily). This gave relief, but the sinusitis recurred in 2 days. He then took 4 gm. of aureomycin, but since this caused heartburn he took 4 additional gm. of terramycin. The entire period of medication was 2 weeks. The sinusitis disappeared, but in the last 4 days of therapy the patient developed a black tongue and mild diarrhea consisting of one mushy stool daily. Since this produced no disability, no therapy or investigation was undertaken. About 3 weeks later weight loss was apparent (8 lb.), and the patient decided to increase weight by a high-calorie diet, which greatly increased the oral intake of fats. At about this time the diarrhea became more frequent, — from 3 to 5 bowel movements daily. The stool was mushy, copious, foamy and not infrequently fatty. At the end of the fifth week the patient was admitted for study.

Physical examination revealed a 10-lb. weight loss and moderately increased peristalsis but no other abnormal physical finding. The blood count and urine were normal. The sedimentation rate (Wintrobe) was 8 mm. Albumin-globulin quantities were normal. A barium enema showed an irritable but otherwise unremarkable colon. The terminal ileal loop was considered questionably narrowed. A small-bowel series showed no further abnormality. The stool consistently showed no pus or blood; however, several specimens stained with Sudan III showed a considerable amount of fat and fatty acid crystals. On an almost fat-free diet the fat content of the stools had fallen to normal.

Culture of the stools failed to reveal any pathogenic organisms. No amebas were present. Special culture technic using Sabouraud's medium failed to demonstrate monilia.

The patient was given a low-fat diet, crude B complex (malt extract) and liver by parenteral injection. Within one week symptoms had completely disappeared and the stools no longer contained fat.

During the next 6 weeks the parenteral administration of liver was twice discontinued experimentally. On each occasion a mild diarrhea resulted after several days. Readministration of the liver stopped the diarrhea. Two months after hospitalization the patient was asymptomatic without therapy.

Case 2. A 37-year-old man was stricken with bulbar poliomyelitis. Before the nature of the disease was recognized he received 3 injections of penicillin. Several weeks later, in the convalescent period, he developed an upper-respiratory infection. He was then given penicillin (400,000 units) daily for 4 days in conjunction with sulfonamides. At about this time he developed a mild diarrhea, consisting of 1 to 3 mushy stools daily. He noted that a high-fat diet aggravated the diarrhea and that after eating fats he occasionally saw fatty globules floating in the toilet bowl after a bowel movement. A fat-free diet lessened the diarrhea, but he continued to lose weight. When seen 2 months after the onset of the diarrhea he had lost 20 pounds.

Physical examination at that time was negative. The sedimentation rate (Westergren) was normal. All other routine blood and urine examinations were similarly normal. The stool, when stained with Sudan III, showed considerable free fat and fatty acid crystals. Small-bowel x-ray films demonstrated a deficiency pattern, with puddling and segmentation. The colon and upper-gastrointestinal x-ray films were normal. There was no pus, blood or protozoa in the stool. Stool culture failed to reveal any pathogenic organisms. The patient was given vitamins and liver by parenteral injection. Improvement was apparent in a few days, and after 2 weeks of a moderately fat-restricted diet the diarrhea had completely disappeared. However, 4 months after treatment overindulgence in fatty foods would still cause 1 or 2 loose stools.

Case 3. A 39-year-old woman developed an acute gastroenteritis and consulted her physician. At that time she had fever (101°), cramps, nausea and vomiting. Aureomycin was prescribed and in 24 hours her condition improved, but the diarrhea continued. In an effort to clear the diarrhea Chloromycetin was used, and the patient was given antibiotics orally (approximately 16 gm.) for 2 weeks. During this entire episode she continued to have 3 to 6 bowel movements daily, which were mushy but not malodorous. After 2 months she was admitted to the hospital for study.

Physical examination at this time revealed only weight loss. The stool contained fat, no pus or blood and moderate amounts of mucus. On culture a heavy overgrowth of *B. proteus* was noted.

Barium colon enema, small-bowel study, upper-gastrointestinal x-ray films and sigmoidoscopic examinations were negative. The sedimentation rate and routine laboratory tests were normal. She was discharged on a vitamin regimen. For about 1 month afterward she continued to have mild diarrhea with occasional explosive episodes, but gradually this decreased. After 4 months of treatment she is now asymptomatic.

Case 4. A 43-year-old physician took 5 gm. of chloramphenicol over a 5-day period for an upper-respiratory infection. About a week afterward he developed a mild but persistent diarrhea. The stools were soft, occasionally foamy and frequently associated with mucus. Mild cramps preceded each bowel movement. Weight loss became noticeable, and after 3 months the patient underwent study. The stools showed considerable mucus, some free fat and some fatty acid crystals but no pus or blood. The blood count and urine were normal. The sedimentation rate was normal. Repeated stool cultures and wet mount studies revealed no pathogenic organisms or protozoa. A barium colon enema and sigmoidoscopic examination were normal. X-ray films of the small bowel revealed considerable hyperactivity.

A low-residue high-calorie diet was advised and followed. This, however, aggravated the diarrhea, and the patient developed night cramps, having several bowel movements each night.

At the end of the fourth month the patient was put on a low-fat diet and given crude vitamin B complex and daily parenteral injections of liver. Within 2 days there was marked lessening of the diarrhea, and the symptoms had greatly ameliorated. At the end of 1 week the improvement was even more pronounced, and the stools were formed.

Discussion

These cases, in addition to the 4 previously reported cases,[1,2] establish an etiologic relation between prolonged diarrhea and the administration of certain antibiotics. The antibiotic agent may be either aureomycin, terramycin or chloramphenicol. Furthermore, in one of the cases presented here the causative drugs were penicillin and sulfonamide in combination. This suggests that the controlling factor is not the specific agent used but rather the range of bacterial destruction in the gastrointestinal tract. Penicillin, the sulfonamides and streptomycin, which do not affect many common forms of bacteria, are alone apparently not sufficient to precipitate this syndrome.

The seat of the diarrhea is clearly the small bowel. The presence of fat in the stools, the tendency of the diarrhea to be aggravated by fat ingestion and the relatively mild nature of the diarrhea are features that are commonly seen in steatorrhea from small-bowel dysfunction. Moreover, in 3 cases x-ray findings pointed to the small bowel as the source of the diarrhea.

The close parallel between these cases and acute tropical sprue is at once apparent. The major features lacking are the secondary deficiency signs and macrocytic anemia. This is probably due to both the short duration of the diarrhea and the high quality of the food eaten by these patients, since, with one possible exception, all the patients are in adequate economic circumstances.

Woods and his collaborators suggest that this syndrome is actually an infection of the gastrointestinal tract with *Candida albicans*. They point out that culture of material removed from the oral, pharyngeal and lingual lesions occurring after antibiotic therapy show growth of this yeast. They are also impressed by the occurrence of monilia in culture of the stools in all 3 of their diarrheal patients, particularly in view of a study by Schnoor in which he found that of 314 stools from persons in the same geographic area only 1 per cent showed a heavy growth of *Candida albicans*.[3] These investigators believe that destruction of other organisms that normally compete with the yeast for nutrient substances allows the yeast to overgrow and become pathogenic, causing clinical infection.

Although this may be true of the oral lesions, it is not readily credible as a cause for the diarrhea.

Several diseases that we now know clearly to be due to dietary deficiencies, such as sprue, glossitis and vaginitis due to avitaminosis B, have in the past been falsely attributed to pathogenic yeasts, as these organisms were found on culture. Subsequently, however, experience has shown that

in these conditions the yeasts were either nonpathogens or at most insignificant secondary invaders. The error arises not only from the presence of monilia in the throat, vagina and stool of apparently healthy persons but more especially from its tendency to grow in areas of disease. Thus it is commonly found in the sputum of patients with proved nonmycotic disease of the lung. Its presence in the stool of patients with diarrhea is apparently without pathogenic significance, since, according to Conant,[4] it is found in quantity in the stools of patients with diarrheal symptoms due to unrelated causes.

It seems entirely possible, therefore, that the yeast found by Woods in the stools of his 3 patients was a result of the diarrhea and not a cause.

Moreover, if there actually were monilial infection of the gastrointestinal tract the commonly recognized signs of infection should be present in both the stools and the blood. Actually, in all cases the white-cell count and the sedimentation rates were normal. In none of our cases did the stools show any pus or blood. At no time did any of our patients run any fever.

Furthermore, our patients treated with liver injections showed a very prompt and dramatic response to therapy, noticeable almost immediately. One could scarcely expect such a rapid improvement if the basic condition was a monilial gastrointestinal infection.

The clinical and laboratory findings in our cases are those of an acute steatorrhea or sprue syndrome, similar in many respects, — even in the finding of monilia in the stool, — to those cases of sprue syndrome from dietary deficiency occasionally seen in practice in poorly nourished persons. The clear-cut response to liver treatment strongly supports this concept.

It is known that certain vitamins of the B complex, including folic acid, are produced by bacterial activity in the gastrointestinal tract.[5] It seems likely, therefore, that the deficiency causing this syndrome is due to wholesale destruction of intestinal bacterial flora.

This syndrome can probably be prevented by the parenteral administration of liver to all patients who are receiving chloramphenicol, aureomycin, terramycin or penicillin-sulfonamide combinations for more than a few days. Parenterally-injected liver is to be preferred to the oral preparations, as in our experience it has shown a much more rapid and pronounced effect.

A special note of warning should be sounded about those patients with ulcerative colitis who are receiving antibiotic therapy. It is common practice to use these agents for long periods of time in the treatment of this disease. Should a sprue syndrome be induced, it is hard to see how it would be recognized as distinct from the primary ailment, and such a complication may well cause considerable deterioration in the patient's condition without the physician's suspicion that a new factor is at work.

Historically, the toxic effects of a drug have usually not become generally known until some time after its beneficial effects have been shown. Thus, it was a number of years after the introduction of aminopyrine that physicians became aware that it could produce agranulocytosis. Cinchophen was in common use for a long period before its hepatotoxic effects were known. This has been true, although to a lesser extent, of both penicillin and the sulfonamides. Consequently, any new drug should be regarded as a tool of uncertain potentialities, and it should not be used to treat light and insignificant ailments.

Summary

Prolonged diarrhea may follow administration of chloramphenicol, aureomycin, terramycin or penicillin-sulfonamide combinations.

The diarrhea closely resembles and is apparently identical with the diarrhea of the sprue syndrome.

It is probably due to a deficiency state secondary to the destruction of the normal intestinal flora.

The diarrhea responds readily to parenterally administered liver, in conjunction with ingestion of B vitamins.

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MEDICAL PROGRESS

MEDICAL USES OF ION-EXCHANGE RESINS

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THE use of the ion-exchange resins in the fields of chemistry, industry and medicine is relatively recent but is becoming increasingly significant. Although their value is established in chemistry and industry, their practical application in the field of medicine awaits further investigation and most particularly depends on the ability of the chemist to synthesize resins capable of specific and predictable performance in vivo. That such tailor-made products will become available appears likely; therefore some familiarity with the nature and mode of action of this group of chemicals is of interest to clinicians at this time.

HISTORICAL BACKGROUND

The principle of ion exchange, or the removal of electrolytes from solution by exchange with electrolytes contained within the structure of the exchange substance, has been utilized since the time of Aristotle.[1] Writings of that period tell of the use of sand to purify water. In 1620 Francis Bacon[2] described a method of purifying sea water by passing it through a series of earthen vessels. However, it was not until 1850 that J. Thomas Way,[3] an English soil chemist, first recognized and described to the Royal Academy the phenomenon of ion exchange. From that time until 1935 very little use was made of the ion-exchange principles because the naturally occurring substances having this property were slow and inefficient exchangers such as earths, coals and cellulose. Distillation and recrystallization provided the chemist with better means of purification and recovery.

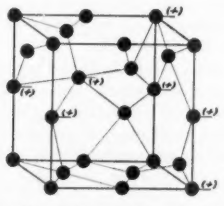

FIGURE 1. *Graphic Representation of Cross-linked, Polymerized Resin Molecule.*

On each of the molecular elements is a functional group providing an ion-exchange site. Between the molecular elements are pores through which ions in solution diffuse to reach exchange sites in the interior.

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However, in 1935 Adams and Holmes[4] first synthesized anion- and cation-exchange resins, and the significant work in the exchange-resin field is dated from that time.

THEORY OF ION EXCHANGE

Resin molecules are insoluble, high-molecular-weight, polymeric electrolytes formed in gel-like particles of varying sizes. A molecule of ion-exchange resin is analogous to a sponge. It is a highly cross-linked polymer, porous in structure, whose architectural elements are stable non-ionizable substances arranged in a lattice pattern. Each of these structural elements has the ability to bind a diffusible ion and to exchange this bound ion for one of like charge under suitable conditions of solution. In this way ions in solution with resin granules may be removed from solution by exchange with ions originally held at the exchange sites.

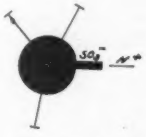

FIGURE 2. *Graphic Representation of a Single Molecular Element with Attached Functional Group and Cation-Exchange Site.*

At the exchange site of each of the polymeric elements of a resin molecule is a fixed functional grouping of opposite charge from the exchanging ions. On the cation-exchange resin the functional group may be, for instance, a carboxyl element with the COO^- portion bearing the negative charge, and the H^+ ion being able to exchange with any other cation to change the functional group from $RCOO^- \cdot H^+$ to $RCOO^- \cdot Na^+$ and so forth. In the anion-exchange resins (all of which are polymerized amines) the functional group is the amine element with the $NH3^+$ portion bearing the positive charge and the hydroxyl OH^- ion being capable of exchanging with any other anion, so as to change the group from $RNH3^+ \cdot OH^-$ to $RNH3^+ \cdot Cl^-$ and so forth.

Exchange Potential

The exchange potential or the efficiency of a resin depends on how many milliequivalents of electrolyte it is able to remove from a solution and how rapidly it does this. Many factors are involved in controlling this potential, and it is toward the control of these factors that the resin chemists are working in order to be able to synthesize specific resins for specific jobs. Some of these factors are listed below.

Pore Size of Molecular Lattice

The size of the pores in the cross-linked resin molecule is probably the most important single factor in the exchange potential.[5, 6] Since the resin acts as an electrolyte sponge, electrolytes must be able to diffuse throughout the substance of the molecule in order to occupy all the exchange sites and saturate the molecule. Large pores permit easy diffusibility and rapid and complete saturation, whereas small pores in tightly cross-linked molecules decelerate diffusion through the body of the molecule and may limit large ions such as vitamins and other organic ions to exchange sites only on the surface of the resin.

Size of Resin Gel Particles

The smaller the particle, as measured by its mesh size, the greater the exchange potential. The mesh size of gel particles is one of the most important determinants of resin efficiency.[7, 8]

Concentration of the Resin in the Solution

The higher the concentration, the greater the exchange potential.

Nature of the Functional Group

If the functional group is a strong acid such as sulfonic, or a strong base, the exchange potential is higher than with less strongly dissociated groupings such as phenolic acid. The potential is lowest of all in the amphoteric naturally occurring resins.

Size of Cations and Anions in Solution

Simple ions such as Na^+ and Cl^- diffuse rapidly from solution throughout the molecular matrix of a resin and saturate all exchange positions available. Larger ions such as organic acids diffuse more slowly and may be able to occupy only surface positions.

Type of Cation and Anion in Solution

The tendency of an ion in solution to displace an ion already on the exchange position depends on two properties:

Valence. Ions of higher valence tend to displace ions of lower valence; that is:

Al^{+++} displaces Ca^{++}
Ca^{++} displaces Na^+.

Atomic weight. If valence is the same, ions of higher atomic weight tend to displace ions of lower atomic weight. That is:

K^+ displaces Na^+
Ca^{++} displaces Mg^{++}.

These factors are important, but it has been found that they are true only of dilute aqueous solution of a resin. At high concentrations or in nonaqueous solutions these tendencies may be reversed. This may account for the failure of animals and man to develop a negative calcium balance when fed cation-exchange resins to remove sodium from the gastrointestinal tract.

The pH of the Solution

Different resins work more efficiently at different pH. This varies with the particular resin.

Cation-Exchange Resins

Most of the currently produced cation-exchange resins are polystyrene polymers with divinyl benzene cross-linkage. There are three main types of cation exchange resins, as determined by the functional group:

Sulfonic acid — $SO3^-{\cdot}H^+$. This is strongly acid and a rapid exchanger. That is, $RSO3^-{\cdot}H^+ + K^+{\cdot}OH^- \longrightarrow RSO3^-{\cdot}K^+ + H20$.

Carboxylic acid — $COO^-{\cdot}H^+$. This is less strongly acid and a slower exchanger. That is, $RCOO^-{\cdot}H^+ + K^+{\cdot}OH^- \longrightarrow RCOO^-{\cdot}K^+ + H20$.

Phenolic acid — $O^-{\cdot}H^+$. This is generally a weak acid and a slow exchanger. That is, $RO^-{\cdot}H^+ + K^+{\cdot}OH^- \longrightarrow RO^-{\cdot}K^+ + H20$.

The ion originally at the exchange site before the resin is put into solution determines the so-called "cycle" of the resin. Thus a carboxylic cation-exchange resin in the hydrogen cycle will have the hydrogen ion at its exchange sites, $RCOO^-{\cdot}H^+$. Some resins are now manufactured that are partially saturated with potassium ions and will be designated, for instance, as a carboxylic cation-exchange resin in the hydrogen and potassium cycles, $— RCOO^-{\cdot}H^+ + RCOO^-{\cdot}K^+$.

Anion-Exchange Resins

Less is known about the anion-exchange resins than about the cation exchangers, as their development and use have been more recent. They are highly polymerized amines in a cross-linked lattice molecule. The ionized functional group is the amine radical, and the exchanger at the exchange site is the hydroxyl ion. Anion-exchange resins are basic

in nature, the more strongly basic of them being the best exchangers. Acid neutralization by the anion exchangers may be by either of two reactions:

Anion exchange: $RNH3^{+}\cdot OH^{-} + H^{+}\cdot Cl^{-} \longrightarrow RNH3^{+}\cdot Cl^{-} + H^{+} + OH^{-}$.

Acid adsorption: $RNH2 + HCl \longrightarrow RNH3Cl$.

It is believed that the weakly basic anion exchangers probably function by acid adsorption, whereas the strongly basic exchangers function by anion exchange.

Regeneration of Ion Exchangers

At present exchange resins are used mainly in industry to remove electrolytes from solution. For the sake of economy it must be possible to reconstitute them after use, and they must be stable enough for prolonged usage.

Cation Exchangers

These are acid elements and may be regenerated by exposure to strong acid, which forces replacement of the cation at the exchange site by the H^{+} ion of the acid solution. That is, $RCOO^{-}\cdot Na^{+} + H^{+}\cdot Cl^{-} \longrightarrow RCOO^{-}\cdot H^{+} + Na^{+}Cl^{-}$.

Anion Exchangers

These are basic elements and can be regenerated by exposure to strong alkali, which forces replacement of the anion at the exchange site by the hydroxyl ion of the basic solution. That is, $RNH3^{+}\cdot Cl^{-} + Na^{+}\cdot OH^{-} \longrightarrow RNH3^{+}\cdot OH^{-} + Na^{+}\cdot Cl^{-}$.

The clinical use of anion-exchange resins has been mostly as an antacid in the treatment of gastric and duodenal ulcers. It has proved an effective neutralizer of gastric hyperacidity and has not resulted in loss of body chlorides or in so-called "acid rebound." This is because the resin is regenerated in the basic media of the intestines, and the chloride picked up in the stomach is displaced by the hydroxyl ion and allowed to return to the body.

Cation-exchange resins partly in the potassium cycle are used to treat cardiac edema without provoking hypokalemia. These resins give up their potassium in the stomach, where they are in a sense regenerated, as gastric HCl forces replacement of the potassium with hydrogen. Then in the alkaline intestines the resin picks up other cations, including sodium and potassium, but since it has left its original potassium in the stomach no potassium deficiency results.

Practical Utilization of Ion-Exchange Resins

Ion-exchange resins have thus far found their greatest application in the fields of analytic chemistry, industry and pharmacy. In medicine their usefulness is just beginning to come under investigation, and their place will be more definitely established when improvements in synthesis result in greater specificity of performance in vivo. Significant progress toward this end is continuing to be made by the resin chemists, and it is likely that in the near future references to these compounds will appear frequently in the therapeutic and investigative medical literature.

Analytic Chemistry

Resins obviate many laborious distillation and recrystallization procedures in this field. Separation and recovery of amino acids, rare earths and isotopes are examples of the application of these resins as a chemist's tool.[5, 6]

Industry

There is a large field of utilization of resins in the industrial world. Resins replace time-consuming and therefore uneconomical distillations and recrystallizations. They are used for softening water and refining sugar. They are used to remove the metals and oils from gasoline, to soften water for carbonated beverages and to remove the organic-acid rind taste from canned fruit juice. Many other examples might be cited.[5, 6]

Public Health

The use of resin deionization units to recover metallic wastes from factory streams, both for public-health purposes and for the economic value of the recovered metals, is increasing in frequency. Such units can also be used to remove radioactive elements from streams and water supplies.[5, 6]

Pharmacology

Resins are invaluable in pharmacology for the separation, isolation and recovery of amino acids and also for the purification of biologic products. They are used for the rapid and complete recovery of antibiotics such as penicillin and streptomycin from synthesizing solutions. They are used to decalcify milk to soften the curd in the preparation of special infant milk products.[5, 6]

Agriculture

Since resins can hold and supply to plants a much greater concentration of various ionic nutrients than can ordinary soil, they are being used in experimental laboratories to speed growth and increase yields.[5]

Qualifications of Resins for Use in Clinical Medicine

Based on considerable animal experimentation and a growing number of reported clinical trials, the following appear to be some of the advantages and disadvantages of the resins — aside from their therapeutic value.

Advantages

They are insoluble and therefore nonabsorbable; they are nontoxic in high doses for prolonged periods; and they are nonirritating in high doses for prolonged periods.

Disadvantages

There is difficulty of administration because of their granular nature and because of the large quantities required for therapeutic effect; there is an element of unpalatability; they may be constipating if administered for a prolonged period (their gel structure absorbs water); there is some unpredictability of the in vivo action of most presently available resins; and cation exchangers tend to induce acidosis.

Ion-Exchange Resins in the Field of Medicine

Adams and Holmes first synthesized anion- and cation-exchange resins in 1935,[4] and a few years later Dock[9] published the results of his work with cation-exchange resins in mice and rats. He noted the lack of any toxicity or interference with growth in spite of massive doses and suggested that resins might be successful in removing sodium from the gastrointestinal tract of man. This, of course, would be of considerable advantage to hypertensive persons on the unpalatable low-salt diet. Work was then begun in various places to determine the efficacy of resins in electrolyte-balance problems.

Cation-Exchange Resins

These resins have been tried principally in three clinical situations: fixation of dietary sodium in the gastrointestinal tract in hypertensive cardiovascular disease[10-16]; prevention of edema formation and potentiation of diuresis in cardiac decompensation, cirrhosis and nephrosis[10-16]; and treatment of hyperkalemia in renal failure.[16, 17]

Fixation of dietary sodium. In 1949 Irwin, Berger and others[13] made an extended and careful balance study on a person who had no hypertension or metabolic or electrolyte imbalance. They showed that in this subject, during periods of resin feeding, the urinary sodium fell markedly, the fecal sodium rose to account for 80 per cent of the dietary sodium and there was no change in the plasma sodium. The resin they used was a sulfonic-acid type. Their figures on the potassium balance paralleled those of sodium, showing a decrease in urinary potassium and an increase in fecal potassium accounting for 68 per cent of the dietary potassium, with no change in the plasma potassium. Their balance studies indicated that during the period of resin feeding there was no loss of sodium, potassium or calcium from the body pool. (However, some instances have been reported[11] of the development of low serum potassium, calcium and magnesium, and the author has stressed the need for careful, patient observation, with replacement therapy when indicated.) This patient developed a compensated metabolic acidosis by the following mechanism: There was a reduced absorption of sodium and potassium from the gut. There was undiminished absorption of acid elements such as chlorides, phosphates and sulfates. This preponderance of acid elements in the blood was compensated by a fall in the CO_2 combining power and a rise in the chlorides. There was no change in pH.

The authors pointed out that their subject had normal kidneys and was able to increase ammonia to excrete the excess acid elements, but they noted that damaged kidneys might not be able to respond sufficiently, whereupon further loss of body base in an attempt to excrete the acid elements would create an uncompensated acidosis.

Prevention of edema formation. These same authors also described the treatment of 2 patients with heart failure and edema, using this same cation-exchange resin. Both patients diuresed without mercurials and did not reaccumulate fluid. They then tried the resin on a patient who had cirrhosis with ascites and edema. This patient diuresed the ascites and edema without mercurials, but developed a low serum potassium and cardiac arrhythmia and died. The authors concluded that the chief hazards of resin therapy were potassium deficiency and acidosis.

A paper by Hay and Wood[10] described a somewhat less precisely studied group of 10 patients with cardiac failure, edema and ascites. Some were given an ammonium carboxylic cation-exchange resin, and some were given the same resin with potassium added to it before administration. These authors felt that the resin feedings blocked gastrointestinal-tract absorption of sodium; sometimes initiated diuresis; and always potentiated mercurial diureses.

They encountered acidosis with administration of each form of their resin, but they believed that the addition of the potassium to the resin structure prevented the development of hypokalemia. They recommended intermittent use of the resin for diuretic effect no longer than four to five days in succession. However, they presented 1 case of continuous use of the resin for 180 days without ill effects. Other reports are in general agreement with the observations and results of these writers.[11, 12, 14-16]

Therapy of hyperkalemia in renal failure.[16,17] The problem of toxic accumulation of potassium in the blood during periods of oliguria or anuria has been most difficult. Various means of dialysis have been proposed to remove this excess of potassium from the blood, but none have proved very practical. A method has recently been described[17] for the removal of potassium from the gastrointestinal tract by use of a cation-exchange resin administered orally and by enema. Some success in lowering the blood potassium was apparent, but what is still needed for successful treatment of this condition is a resin

with a high specificity and exchange potential for the potassium ion. Such a resin has not yet been reported but doubtless will be developed.

An excellent discussion of cation-exchange-resin therapy by Dock has recently appeared.[11]

Investigative use of cation-exchange resins. Illustrative of a diagnostic use to which cation-exchange resins are being put is a recent report[18] describing the use of a cation resin with a quinine cation attached to determine the presence of free gastric acidity without intubation. This author used a carboxylic cation resin with a quinine cation at the exchange spot. The H^+ ion of the free acid in the stomach displaced the quinine cation, which was then absorbed and later excreted in the urine, where its presence was determined by fluorescing the urine with ultraviolet light.

An interesting and useful application of the cation-exchange resin has been developed by Dotti, Paparo and Clarke.[19] They have found that the decalcification of bone specimens preparatory to sectioning and staining for microscopical observation can be carried out much more rapidly with an exchange resin than with the conventional acid-decalcification method. Furthermore, the stained slides were clearer in morphologic detail and superior in stain quality to those of acid-treated specimens.

Some work has been done by Steinberg[20] on the use of cation-exchange resins to decalcify blood and thus inhibit coagulation. Resin-treated blood will stand indefinitely without coagulating. Animal experiments have shown[5] that blood let from rabbits and passed through a cation exchanger can be returned to the rabbits without ill effects. Blood specimens from horses and pigs, — normally incompatible, — if treated with a cation exchanger seemed to be rendered compatible. Further investigation into resin-treated blood may solve some of the problems of blood storage and compatibility.

Anion-Exchange Resins

These resins have their main clinical application in the treatment of gastric and duodenal ulcers. It has been generally accepted that the etiology of ulcer pain, — if not the formation of the ulcer itself, — is related to the action of pepsin and hydrochloric acid digesting away the mucous covering that protects the gastric mucosa and then eroding the mucosa itself. Pepsin acts as an enzyme in protein hydrolysis but can function only at a low pH. Therefore, removing the pepsin or inactivating it by raising the pH of the gastric contents helps to prevent formation and promote healing of ulcers. An ideal antacid should have the following properties: It must be insoluble and therefore nonabsorbable; it must be neutral in aqueous medium but capable of neutralizing acid; it must be nonirritating to the gut; it must not alter the acid-base balance of the body; it must not cause diarrhea or constipation; it must not alter mineral metabolism (no loss of chlorides, phosphates and so forth, and no acid rebound); and it must not alkalinize the urinary tract. It has been found that suitable anion-exchange resins fulfill these qualifications.[7, 8] The resin rapidly adsorbs stomach acid and carries it into the intestinal tract, where in an alkaline medium it releases the acid ions back to the body. The resin inactivates pepsin by having raised the pH of the stomach and also by directly adsorbing and removing it to some extent. Clinical reports[7, 8, 21-27] indicate that with resin therapy relief of pain and healing of demonstrated lesions appear to be at least as rapid and complete as with any of the other ulcer regimens.

Favorable results have been reported with the use of anion-exchange resins in the treatment of heartburn in pregnant women.[28] Anion-exchange resin sprinkled locally on the skin around an entero-abdominal fistula will allay the irritation caused by seeping digestive juices.[29] Both anion- and cation-exchange resins have been reported to be of value in the isolation of virus matter for study and transmission.[30, 31]

Summary

Ion-exchange resins are briefly described as regards their history, physical structure, principles of action, factors controlling their performance and practical and theoretical uses and potentialities in chemistry, industry and medicine. Ion-exchange resins have the property of selectively removing electrolytes from solution. They are themselves stable, insoluble, nontoxic and capable of being regenerated. They are of proved value in industrial processes, chemical analysis and pharmacologic purifications. They have shown some promise in clinical medicine[11, 32] — notably: in fixing dietary sodium in the intestinal tract; as an aid in the control of edematous states; in the treatment of hyperkalemia; and in the management of gastric and duodenal ulcers.

In the field of clinical medicine the resins have certain limitations and disadvantages in their present stage of development. These are: lack of specificity of action, relative unpredictability of action in vivo, production of acidosis — especially if renal insufficiency exists, production of hypokalemia, and difficulty of administration because of bulk and unpalatability.

According to the resin chemists, work is progressing rapidly toward the development and economic synthesis of resin types that will obviate the previously listed drawbacks of presently available compounds and will provide both industry and medicine with specific and reliable aids.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 37351

PRESENTATION OF CASE

A fifty-year-old woman entered the hospital for evaluation of an abnormal shadow discovered in a routine x-ray film of the chest one week previously.

For about sixteen years before admission the patient had complained of postnasal discharge and productive morning cough and had treated herself with oily nose drops. She had frequent upper-respiratory infections and several times each winter would take to her bed with cough and fever diagnosed as "chronic bronchitis." Nine years, five years and five months before admission she was hospitalized because of attacks of right-sided "lobar pneumonia," which responded to chemotherapy and antibiotics. About six months before admission she had an attack of "virus pneumonia."

Fifteen months before admission she had a small hemoptysis of bright-red blood that welled up suddenly from her throat after some difficulty in swallowing a cough drop. There was no associated pain, fever or malaise of any description. A chest film taken by her physician was said to have shown a "cloudy condition." Two forty-eight-hour sputum cultures were negative for acid-fast bacilli. The patient began to keep a daily temperature chart, which remained within normal limits at all times. A month after the hemoptysis the patient was studied at this hospital as a medical out-patient. Physical examination was unremarkable. The blood and urine were within normal limits, but the sedimentation rate was 41 mm. per hour. The films taken in another hospital were reviewed, and the findings were believed to be consistent with old healed pulmonary tuberculosis. Bronchoscopic examination was considered but was deferred because the bleeding had stopped.

Periodically x-ray films were taken at a tuberculosis sanatorium and the reports sent to her physician. In addition, she made periodic visits to the Pulmonary Clinic. No essential changes were noted in the x-ray findings until six weeks prior to admission, at which time a large shadow at the right base was noted. Films taken here two weeks later showed a rounded mass 7 cm. in diameter projecting from the wall of the anteromedial right base. This was independent of both the heart and

the diaphragm. The upper right lung field showed mottled density, especially at the periphery. The diaphragm was normal in shape and contour. The left lung field, heart shadow and great vessels were unremarkable (Fig. 1 and 2).

The family history revealed that the patient's mother, who died at the age of eighty of arteriosclerosis and hypertension, had had repeated small hemoptyses throughout her life. Two half-sisters died of pulmonary tuberculosis forty-one and forty-three years before the patient's admission.

On physical examination an area of dullness was found over the right anterior chest, associated

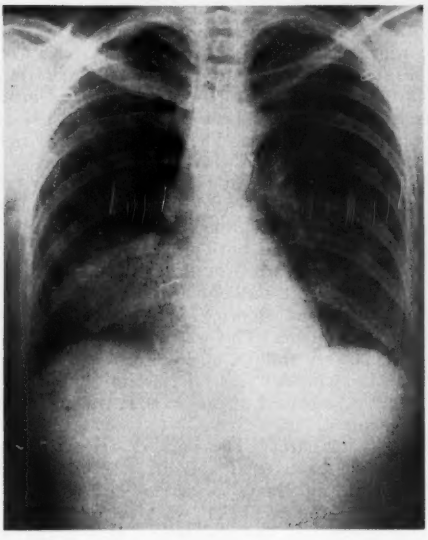

FIGURE 1.

with decreased whispered voice and breath sounds and tenderness to direct palpation. The lungs were otherwise clear and the heart normal. The margin of the liver and tip of the spleen were just palpable below the costal margin. Grade I to II hypertensive retinopathy was present. There were large varicosities on both lower extremities.

The temperature was 99°F., the pulse 80 and regular and the respirations 20. The blood pressure was 180 systolic, 110 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 13.0 gm. and a white-cell count of 5600, with 66 per cent neutrophils, 24 per cent lymphocytes, 8 per cent monocytes, 1 per cent basophils and 1 per cent eosinophils. The sedimentation rate was 50 mm. in one hour. A cytologic examination of the sputum was negative for malignant cells.

X-ray examination of the chest showed the mass in the right thorax to have definitely enlarged. Fluoroscopically it appeared to move synchronously with the lower anterior chest wall. Barium-enema

FIGURE 2.

and barium-swallow examinations were negative. There was no evidence of herniation through the right leaf of the diaphragm. The kidneys appeared to be normal. The spleen was larger than normal, and the liver was noted to be low in position.

After an uneventful period of observation, an operation was performed on the seventh hospital day.

DIFFERENTIAL DIAGNOSIS

DR. EDWARD D. CHURCHILL*: A fifty-year-old woman was admitted to the hospital, as so many people are these days, for an evaluation of an abnormal shadow discovered in a chest film.

For about sixteen years she had had vague respiratory symptoms. That is rather typical of what repeated questions finally elicit from a patient and is probably irrelevant. I do not think the oily nose drops had anything to do with this patient's condition. Like almost everyone, she had frequent

*Chief of Surgical Services, Massachusetts General Hospital.

upper-respiratory infections, but unlike most others she took to her bed several times each winter with chronic bronchitis. The patient also disclosed the fact that fifteen months before admission she had what a physician called hemoptysis. The film of the chest taken by her physician was reported as cloudy. This means nothing; perhaps she breathed when the film was taken.

The patient began to keep a daily temperature chart, indicating that she was becoming disturbed about her condition, but whether this was because she thought the physicians believed she had something or because she felt ill is hard to say. At any rate the temperature-taking yielded no information. A month after the hemoptysis and fourteen months before admission, she came to the Out Patient Department. Examination was negative except for a sedimentation rate of 41 mm. per hour. I have not the slightest idea what that means. The x-ray findings were consistent with an old healed pulmonary tuberculosis. Bronchoscopy was considered, — I presume because of the hemoptysis, — but was deferred. Bronchoscopy is a very important procedure when a patient spits up blood.

X-ray films were made periodically at a local tuberculosis sanatorium and the reports were sent to her physician. In addition she made regular visits here to see Dr. Pittman in the Pulmonary Clinic. Nothing was found in the chest until six weeks prior to admission. That is not quite correct, however, as she did show a shadow prior to that time.

After admission to the hospital the physicians dug out the fact that the patient's mother lived to a ripe old age and had had small hemoptyses all her life. There were also two half-sisters who died of pulmonary tuberculosis. I do not know through which side of the family they were related, but because the mother lived to a ripe old age I can assume that perhaps they were her mother's daughters, so that there was familial distribution of tuberculosis. Nothing abnormal was found on physical examination.

The patient was said to be in no distress. You cannot make me believe that. I think she had the "daylights scared out of her." I do not think she had any pain, but one cannot take his own temperature, have hemoptysis and run to physicians as this woman did without being in some mental distress.

All this reduces the problem to a guessing game on x-ray shadows, and I am delighted to have the radiologist hold forth.

Dr. Joseph Hanelin: We have chest films, made elsewhere, dating back eight years. In the films taken eight years before admission there is nothing of note other than calcific and fibrotic scars in the right lung of rather minimal extent. The heart and diaphragm appear normal. On carefully perusing the old films, I think the first evidence of disturbance in this patient's chest is shown on films taken a year before admission, at which time there is just visible at the right base, along the heart margin and through the heart shadow, a mottled density that had not been present previously.

Dr. Churchill: How about the apex?

Dr. Hanelin: I do not think the lesion there had progressed to the apex. In films taken four months and seven months later there is evidence of enlargement of the density at the right base. No lateral views were taken at that time. In the films taken a week before admission, when the lesion was first discovered, it is of large size. In the films made on admission, the mass lies anteriorly on the right and appears, particularly in the oblique view, to be distinctly separate from the diaphragm (Fig. 1 and 2). On fluoroscopy it moved synchronously with the anterior chest wall, and in all the films in which the mass attained any size it seems to be consistently confined to the level of the third, fourth and fifth ribs anteriorly. Also noted in the examination a week before entry is the first appearance of transverse linear streaks in the right upper lung. There is also some suggestion of an enlarged lymph node at the right hilus. As to the statement of no evidence of herniation, a shadow at this level should always be regarded as a possible omental hernia until proved otherwise. Barium-enema and barium-swallow examinations were made. In the presence of omental hernia the transverse colon and stomach will usually be pulled toward the hernia. This was not true in this case. In the last set of films, made three weeks after the first Massachusetts General Hospital examination, further enlargement of the mass at the right base has occurred.

Dr. Churchill: The signs of omental hernia through a parasternal aperture, the foramen of Morgagni, are always looked for in relation to a lesion but are present only when the omentum has been drawn up into the chest. This would not exclude a diagnosis of intrathoracic protrusion of properitoneal fat.

Dr. Hanelin: No; not at all.

Dr. Churchill: I dislike discussing this case, because I see so much harm done these days from using clinicopathological-conference technics on living patients before the course to be pursued is definitely charted. I would like to say for the record that I know I do not know what this shadow represents. There should be no pretense. Why is that important? Because too much emphasis is placed on making guesses about what the shadow may represent, instead of arriving at a clear-cut decision as to what course of action is advisable. The patient cannot understand why, after x-ray films have been made, the physician does not seem to know what is there. The physician gets his mind centered on the precise identification of a shadow rather than on what should be done with a par-

ticular patient under these circumstances. As a result, patients that I see in consultation are likely to be in an antagonistic, thoroughly bewildered and confused state of mind.

It is very simple to explain to the patient something about the type of evidence that the x-ray film provides. Very often I use the remark: "You know, the x-ray examination does not tell us precisely what is wrong." This comes as a surprise, because by this time the patient has been forced to the conclusion that the x-ray is precise but the doctors are hazy. "Do you remember," one may continue, "when somebody put his hands in front of a light and cast a shadow on the wall and made you think it was a horse? That's what we are dealing with — a shadow picture." Then the patient begins to understand why his physicians seem a bit confused. In the meantime the consultant is making up his mind about what he will recommend under the circumstances. He should not hold a clinicopathological conference in front of the patient but should say: "I don't know what this is, but I do know what to do about it."

There is no question whatsoever about what should have been done about the patient under discussion. I must confess to an almost complete lack of interest in guessing what produced the shadow. There is no train of logical reasoning or experience that might enable anyone to make a preoperative diagnosis in this case. With a lump that is accessible to palpation, certain physical signs may help determine its nature — hardness, firmness, mobility and so forth. One cannot palpate a shadow. If lumps in the chest could have been felt, chest surgery would have developed more rapidly.

Having warned against guessing games in front of the patient, we can proceed to the conventional practice of these conferences. The position and size of the mass are important. We know that she had had a primary tuberculous infection; a Ghon tubercle lies behind the shadow. Possibly she, along with her half-sisters, received a dose of tubercle bacilli from the blood-spitting mother. Is the shadow an old or a fresh tuberculous infiltration? It is hard for me to interpret it as tuberculosis. Occasionally a small localized pleural effusion will occur in tuberculosis, but that is not likely in this case, particularly in the presence of an established primary infection dating back many years. I do not believe that the present condition was connected with the tuberculosis but that the patient had inactive tuberculosis in addition.

I have already said that the mass could represent a hernia in the diaphragm, despite the studies that suggest otherwise. If it was found to be a hernia through the foramen of Morgagni, it would have contained properitoneal or propleural fat, not omentum or bowel. Could it have been a simple fatty tumor? Yes; it may have been a lipoma. Against that is the evidence of increase in size. I do not think it is logical to consider it a thoracic lipoma, because it was expanding too rapidly.

Was it malignant tumor? I think not. The position is against it; it was not in the lung by x-ray examination, was it?

Dr. Hanelin: There were two schools of thought. It certainly was in the thoracic cavity, but whether it was in the pleural space or in the lung parenchyma was seriously debated.

Dr. Churchill: I do not believe a shadow in such a position was in the lung. One might be fooled, however. It may have been a tumor close to the lung, but it does not appear to be based on the lung. If it was not based on the diaphragm or on the lung, where was it based? That brings up two other diagnoses. Its position is a favorite one for a pleuropericardial cyst. Such cysts may be completely cut off from the pericardium and contain what we loosely call spring water, — it actually looks like spring water. Such cysts do not grow as rapidly or expand as this shadow had done. Moreover, it is large for the usual pleuropericardial cyst that occupies this angle. However, as you look through the films the only point at which the shadow is attached, — and the oblique film shows it very nicely, — is on the lateral surface of the pericardium, so anatomically it could be a diverticulum of the pericardium, rather than a pleuropericardial cyst that had been embryologically pinched off from the pericardium.

For the record I shall make the diagnosis of pleuropericardial cyst.

Dr. Tracy B. Mallory: I am in hearty agreement with much that Dr. Churchill has said about the comparative unimportance of a correct preoperative diagnosis in comparison with the great importance of a decision concerning what to do about the lesion. In the course of about a score of years since Dr. Cabot's retirement the emphasis in clinicopathological conferences has shifted from primary interest in diagnosis to explanation of how the demonstrated pathologic lesion or lesions explain the patient's clinical course and symptoms. The latter may sometimes be a difficult task for the pathologist because the evidence is not always adequate.

Dr. Helen S. Pittman: This patient was referred to us somewhat over a year before admission because she had spit blood. She actually had spit less than a teaspoonful of blood, and she had stopped bleeding when we saw her. We thought she had bled from around a little bit of calcium in an old tuberculosis lesion, and we were not very much worried. If she spit more blood, she was to come back at once; otherwise she was to come back in a few months for a checkup. When

she came back for the checkup we found that she had spit no blood and was all right. She came back six months later with the films showing this large mass and it was decided to send her into the hospital. On physical examination there was one thing that impressed me: that is, that she spit a small amount of sputum into the cup each day and there was a small bit of blood in the one specimen I saw. She had marked rib tenderness over the shadow. Dr. Kane is the one who really "carried the ball."

Dr. Lewis W. Kane: I have nothing to add except that she was very apprehensive because of the family history of tuberculosis. When she had a hemoptysis the size of a dime, she was sure she had tuberculosis. The shadow along the right margin of the heart was mentioned, I believe, when the serial x-ray films were taken. But she had had a bout of pneumonia on that side just before that, and there was some question whether this was not a residual condition. Unfortunately, I did not see her until one year later. By that time the shadow had increased so markedly in size that she was sent to the hospital for thoracotomy.

Dr. Edward B. Benedict: I would not defer bronchoscopy just because bleeding had stopped. I should like to bronchoscope a patient of this sort with a mass and with hemoptysis on the basis that she very likely had a carcinoma.

Dr. Pittman: The bleeding occurred a year before any shadow was identified in the chest, and there was only one episode of a small amount of bleeding, which we thought was from the calcium. All we could see was calcium.

Dr. Bernard Jacobson: Are you not slightly worried by the spleen's getting bigger?

Dr. Churchill: I have no evidence that it was enlarged.

Dr. Hanelin: We were not at all sure that the spleen had changed in size. Eight years before admission the spleen also looked somewhat oversized.

Dr. Lamar Soutter: We believed there was some urgency in operating on this woman, because we thought the shadow in the lung was probably a malignant tumor.

Clinical Diagnosis

Malignant tumor of lung.

Dr. Churchill's Diagnosis

Pleuropericardial cyst.

Anatomical Diagnosis

Malignant lymphoma, reticulum-cell sarcoma type, of lung.

Pathological Discussion

Dr. Soutter: When the chest was opened the lung was densely adherent to the chest wall, with thick edematous adhesions. As we severed these we found a tumor lying in the middle lobe. It had invaded both the upper and lower lobes and the anterior chest wall. We biopsied the tumor. The pathologist confirmed the fact that it was a malignant neoplasm. We believed a resection would not benefit the patient, as there was not only local invasion but distant metastases to the peristernal lymph nodes. Therefore nothing further was done.

Dr. Tracy B. Mallory: A biopsy specimen was taken that showed a frankly malignant tumor that at one point was invading striated muscle. I assume from Dr. Soutter's description that it was an intercostal muscle rather than the diaphragm.

Dr. Soutter: That is correct.

Dr. Churchill: The earliest film that showed a shadow was taken how long before admission?

Dr. Benedict: About sixteen months.

Dr. Churchill: That could have been the beginning.

Dr. Benedict: That was about the time she had the hemoptysis.

Dr. Churchill: Was there ever hemoptysis that would have permitted localization by the bronchoscope?

Dr. Benedict: I do not know.

Dr. Hanelin: I think one would have to look very closely and be very suspicious to see an abnormal shadow in that film. Other views and grid films would have been helpful. Six months later there was a very definite shadow that was interpreted as pneumonia.

Dr. Benedict: Bronchial washings might have shown more than the sputum. I cannot quite agree with your philosophy, Dr. Churchill. When one raises the question of cancer in a patient's mind, the sooner he operates the sooner he has put the patient's mind at rest.

Dr. Churchill: You misunderstood my point. I agree with you completely. However, when the question of an abnormal shadow comes up and no further evidence can be obtained, one should concern himself with what should be done rather than a precise definition of what it is.

Dr. Benedict: The question of tumor had been raised.

Dr. Churchill: If one argues about the identity of the shadow, he loses his opportunity to do the right thing.

Dr. Pittman: Here we missed our opportunity to identify anything in the film.

Dr. Churchill: There was not much to see.

Dr. Pittman: It can be seen there now, but it was not noted until a year after the films were taken.

Dr. Mallory: The histologic examination showed without any question that the tumor belonged in the lymphomatous group. There was some difference of opinion among members of the staff concerning which subtype of the lymphomatous tumors it should be placed in. I personally

thought it should be called a reticulum-cell sarcoma, although the possibility of the sarcomatous form of Hodgkin's disease could not be absolutely eliminated. Some authorities like Dr. Philip Custer doubt that there is a true distinction between these two forms.

DR. HANELIN: Was any lymphatic spread evident in the right upper lung?

DR. SOUTTER: No, I do not think so. The right upper lobe of the lung was somewhat compressed by the tumor, but except where it had been locally invaded there was no tumor within it or in the interlobar nodes.

DR. MALLORY: It would be impossible, from the small specimen we received, to decide whether or not this tumor involved the lung tissue. We shall have to take the surgeon's gross exploration for settlement of that issue.

DR. SOUTTER: I gave you two specimens, one from the chest wall and one from the lung.

DR. MALLORY: There was no recognizable lung tissue, grossly or microscopically.

DR. CHURCHILL: I do not know whether anyone present heard Tallulah Bankhead's version of "Casey at the Bat." Casey went home after having struck out. His wife asked him what happened. All he could say was: "I don't know; I just don't know."

CASE 37352

PRESENTATION OF CASE

A forty-two-year-old man was admitted to the hospital because of oliguria.

Four weeks before entry he received 10 gm. of sulfadiazine a day for three days because of a sore throat and acute tonsillitis, which completely subsided within one week. Two weeks before entry he noted weakness, puffiness of the face and severe lumbar pain, for which he was admitted to another hospital. He was anuric for the next twenty-four hours. After this he complained of severe headaches, the blood pressure was elevated and the urine contained blood and albumin. The blood pressure apparently returned to normal three days later. Five days before entry he developed blurring of vision, mental confusion, anorexia and muscular twitching. On the day before entry he voided "more" than on previous days. He received no intravenous therapy.

There was no history of any significant illness in the past.

Physical examination revealed an overweight, confused man with thick speech and gross twitching of the extremities. There were enlarged, inflamed tonsils, a Grade II aortic systolic murmur, signs of a small right pleural effusion and + pitting edema over the sacrum and ankles. The fundi were negative.

The temperature was 99°F., the pulse 96 and the respirations 20. The blood pressure was 150 systolic, 90 diastolic.

The urine was acid, had a specific gravity of 1.020 and gave a ++++ test for albumin; the sediment contained 200 red cells, 25 white cells and a few waxy and granular casts per high-power field. Examination of the blood showed a hemoglobin of 10.3 gm., a white-cell count of 14,600, with 88 per cent neutrophils, and a hematocrit of 27 per cent. The nonprotein nitrogen was 265 mg., the blood urea nitrogen 244 mg., the calcium 5.8 mg. and the phosphorus 22.2 mg. per 100 cc.; the potassium was 7.0 milliequiv., the sodium 137.4 milliequiv., the chloride 92 milliequiv. and the carbon dioxide 14 milliequiv. per liter. There was 3.0 mg. per 100 cc. of acetylated sulfonamides in the serum but no free sulfonamides. An electrocardiogram showed a normal rhythm at a rate of 90, a PR interval of 0.28 second and a QRS interval of 0.10 second. Cystoscopic examination with ureteral catheterization revealed no blockage of pelves or ureters.

Because of marked nausea the patient was fed by stomach tube. By this route he received 1500 cc. of fluid, later raised to 2500 cc., per day, containing approximately 2000 calories of glucose and fat. Moderately severe diarrhea developed. On the fourth and fifth hospital days a pericardial friction rub was heard, but his general physical condition remained unchanged for the first eight days. He received 10 mg. of ACTH (adrenocorticotrophic hormone) a day from the fourth to the sixth day, with a satisfactory eosinophil response; 250 cc. of packed red cells on the sixth hospital day; and 10 gm. of sodium bicarbonate orally a day from the sixth day on.

There was virtually no urine output for the first two hospital days, but thereafter he voided 200 cc. per day and on the eighth and ninth days 360 and 400 cc. respectively. On the fourth day the urine had a specific gravity of 1.017 with a pH of 5, gave a ++++ test for albumin and contained 20 red cells and numerous granular casts per high-power field in the sediment. The nonprotein nitrogen was 330 mg. per 100 cc. and the potassium 8.6 milliequiv., the chloride 93 milliequiv., the sodium 122 milliequiv. and the carbon dioxide 12.2 milliequiv. per liter. On the eighth hospital day the patient began to have slight respiratory distress, and a few rales were noted at the right base. On the ninth day the nonprotein nitrogen was 285 mg. per 100 cc., the potassium 7 milliequiv. per liter and the carbon dioxide 19.7 milliequiv. per liter. The respiratory difficulty increased, and the temperature was 100.4°F., the pulse 108 and the respirations 25 to 30. He died on the tenth hospital day with severe respiratory distress, shortly after a tube feeding.

Differential Diagnosis

Dr. Charles H. DuToit*: Are there any x-ray films to show? The only thing I am interested in is the degree of congestive failure and the amount of pleural fluid that was mentioned in the physical examination.

Dr. Joseph Hanelin: There is a single chest examination, which shows a few horizontal streaks at each base that could be due to atelectasis. The heart is slightly prominent in the left-ventricular area.

Dr. DuToit: In summary, this is the case of a forty-two-year-old man who died of uremia following acute renal failure. There was nothing in the history to suggest any pre-existing kidney disease; in fact, the negative fundi tend to rule out the presence of chronic glomerulonephritis, severe hypertension, chronic pyelonephritis or even polycystic kidneys prior to the terminal episode. Cystoscopic examination with urinary catheterization seems to rule out any gross obstructive lesion of the lower urinary tract. Only one finding points away from acute disease as the whole explanation for the situation: that is, the moderate degree of anemia that the patient had on admission. In some cases of glomerulonephritis in children a rapid development of a moderate degree of anemia has been observed, but I do not believe that is seen frequently in adults, either with acute glomerulonephritis or with lower-nephron nephrosis. Before leaving the question of chronic renal disease, I might mention that certain cases of multiple myeloma with Bence–Jones proteinuria may decompensate rather quickly, simulating acute renal failure with varying degrees of oliguria and anuria. In this case the albumin was described as ++++. If this really was ++++ the albumin would be somewhat in excess of that which is usually seen in acute nephropathies. But this was not a quantitative determination, so it does not seem wise to put too much emphasis on this point.

I might mention, in passing, the possibility of subacute bacterial endocarditis with renal infarction or with either a diffuse glomerulonephritis or a focal nephritis. However, the only possible suggestion of such a condition is a systolic murmur in the aortic area. Infection in the urinary tract was not suggested in any way.

I am forced to relate the renal failure to the events that occurred four weeks before entry. Two obvious possibilities come to mind. The first is acute glomerulonephritis following an acute streptococcus infection of the upper respiratory tract. There are several features that support such a possibility. There was a latent period of about two weeks before the onset of symptoms. Puffiness of the face and severe headaches occurred rather early in the disease — I assume probably before the uremia was too marked and without a great degree of elevation of the blood pressure. The persistence of a fairly high specific gravity of the urine — 1.020 of the first and 1.017 of the second — is quite compatible with acute nephritis. However, in acute glomerulonephritis, persistent nearly complete anuria leading to death in uremia is quite unusual. It apparently can occur and has been described, but it certainly is the exception rather than the rule.

The second possibility, of course, is that the sulfadiazine was in some way responsible for the renal lesion. The problem is somewhat difficult, in that sulfadiazine may injure the kidney in several different ways and possibly in various combinations of these ways. The sulfadiazine crystals may cause mechanical blockage of the kidney tubules. If 10 gm. a day was the correct dose, that was quite high and might conceivably lead to such trouble. The onset with severe lumbar pain would also suggest mechanical blockage. However, the long latent period, the absence of crystals in the urine and the negative finding at cystoscopy would be very much against it.

The question whether lumbar pain helps in the differential diagnosis intrigues me somewhat. In the textbooks it is described with all the kidney lesions that one should consider. I should think it would point more toward damage due to sulfonamides than toward glomerulonephritis. Although such pain is said to be present in cases of severe fulminating glomerulonephritis, I myself have never seen it.

Perhaps the most important type of sulfonamide injury is lower-nephron nephrosis, in which Dr. Mallory[1] is much interested. From a statistical standpoint, this would seem by far the most likely explanation of the over-all clinical picture. In lower-nephron nephrosis persistent anuria is the rule in a high percentage of cases. It is true that the patient survived some twenty-four days after the onset of symptoms; that is somewhat longer than is mentioned in most of the published cases. It is said that recovery from lower-nephron nephrosis usually begins about ten days after the onset, and if the patient can be tided over the first ten days his chances of recovery are considerably better. I am assuming that this was a very severe lesion. The treatment used in this case has been popular for only three or four years. This consists of cautious rather than excessive hydration in conjunction with dietary manipulation designed to minimize tissue destruction and to cut down the amount of nitrogenous waste material and to minimize a rise in the serum potassium. In a certain number of cases a high potassium level is the cause of death. This patient was treated in such a way as to minimize

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these complications as far as possible. The main exception to such a diagnosis would be the relatively high specific gravity of the urine. In most of the cases reported in the literature and in most of the cases that I have seen, the specific gravity has been somewhat lower, — about 1.010 during most of the disease. Facial edema is likewise said to be rather unusual as an early manifestation; in this case it was one of the first signs that the patient noted. There were no intensive attempts at flushing the kidneys by excessive fluid intake,—which makes one wonder why puffiness of the face appeared so early in the course. The latent period seems to have been somewhat longer than is usually seen in lower-nephron nephrosis after administration of sulfonamides. On the other hand, lower-nephron nephrosis may have a somewhat insidious onset, so the latent period, as cited in the protocol, may not have been accurately described.

Lower-nephron nephrosis is a disease that has a definite pathological significance. It is also thought to represent a physiologic disorder that is different from that of acute glomerulonephritis. In acute glomerulonephritis the physiologic lesion is thought to be failure of filtration; hence the glomerular filtration might be impaired, leading to an inability to excrete water and other components of the urine. One theory of lower-nephron nephrosis explains the defect as one of a back diffusion of all urinary constituents into the diseased area, which comprises the distal convoluted tubules and nearby areas, as into a sponge. That concept has not been generally accepted, but it does make lower-nephron nephrosis a somewhat different situation, physiologically as well as pathologically, from what is seen in other types of kidney damage.

Other lesions have been described as following sulfonamide medications. Polyarteritis — one had better say polyvasculitis — has been seen in the kidney by Rich[2,3] both in man and in experimental animals. It is somewhat hard for me to determine how much of the so-called interstitial nephritis is the interstitial reaction that is seen in lower-nephron nephrosis. In one case reported by More[4] there was a glomerulitis and a diffuse nephritis that were described as quite different from any other known renal lesion.

Going back over the protocol to see if I can pick up any clues that would help me to decide, I find that by and large nearly all the clinical and laboratory features are common to all the conditions that I have considered. Red-cell casts would favor glomerulonephritis; the pigment casts would point to lower-nephron nephrosis. One might briefly mention the finding of acetylated sulfonamide in the blood almost four weeks after the patient had received the sulfonamide. Sulfonamides are cleared by the kidneys very rapidly, somewhat in the manner in which urea is cleared. Acetylated sulfonamides are cleared perhaps even more quickly. One would expect that if a considerable latent period had existed between the administration of the sulfonamides for the sore throat and the onset of the kidney disease there would have been time for the blood level to reach approximately zero. I do not believe the blood sulfonamide has any significance other than that of shortening the latent period or possibly pointing to pre-existing renal disease. I do not believe it could be used as a diagnostic indication that the kidney damage was necessarily due to the sulfonamides.

In conclusion, I shall put lower-nephron nephrosis as my first choice and acute glomerulonephritis as a rather close second. Aside from the few features that favor a glomerulonephritis, there seems to be a much greater probability that lower-nephron nephrosis would explain the over-all clinical picture.

Dr. Alexander Leaf: I might mention the opinion on the service. The acute onset of headaches, elevated blood pressure, puffiness of the face and anemia coming on about two weeks after an upper-respiratory-tract infection suggested to us that the best bet was acute glomerulonephritis that had developed the rather unusual complication of anemia. When we received the report of the acetylated sulfonamide in the serum we felt less secure about the diagnosis and wondered if the picture might represent a lower-nephron nephrosis probably due to "sulfa" sensitivity.

The treatment for this condition is the management of acute renal insufficiency, regardless of the underlying cause of the cessation of renal function. The aim is to replace extrarenal fluid loss (and electrolyte loss, if any) but otherwise to avoid overhydration, and to reduce protein catabolism to a minimum so that the rate of accumulation of toxic end-products of protein catabolism is decreased. This latter aim is achieved by supplying calories from nonprotein precursors, glucose and fat. When such therapy is instituted one's hope is that the patient will be kept alive until regeneration of kidney tissue is sufficient to permit resumption of renal function and urine flow. This usually requires seven to twenty-one days.

At the time of the unfortunate terminal episode we had hopes of perhaps being over the hump; the nonprotein nitrogen and serum potassium had dropped and urine flow seemed to be increasing.

Clinical Diagnoses

Acute nephritis with anuria.
Aspiration pneumonia.
Uremia.

Dr. DuToit's Diagnosis

Lower-nephron nephrosis.
?Glomerulonephritis.

Anatomical Diagnoses

Acute glomerulonephritis.
(Uremia.)
Aspiration bronchopneumonia, bilateral.
Pericarditis, acute fibrinous.

Pathological Discussion

Dr. Tracy B. Mallory: One point that has interested me considerably in regard to the comparative symptomatology of lower-nephron nephrosis and acute glomerulonephritis, — although I have never been able to find any explanation for it, — is that the convulsive phenomena that are so common in glomerulonephritis seem to be relatively unusual in lower-nephron nephrosis. Possibly the twitching that was observed in this patient might be considered a slight straw in the wind in the direction of glomerulonephritis, although I am not certain how much reliance could be placed on such an observation. It certainly does not permit a definitive distinction between the two processes.

At autopsy this patient showed very much enlarged kidneys, and, as is commonly the case, no very accurate diagnosis of a type of renal disease could be made on the basis of their gross appearance. When microscopical sections became available, it was at once apparent that there was a very extensive severe and acute diffuse glomerulonephritis. There were relatively minor changes in the proximal convoluted tubules, — a vacuolization of the epithelial cells in that segment of the nephron, which is a very common finding in glomerulonephritis and would be quite unusual in a lower-nephron lesion. There were no clearly degenerative changes in the lower nephrons and no vascular lesions.

The heart weighed 450 gm., which is about at the upper limit of normal size; it might conceivably represent a very slight degree of hypertrophy. There was a rather extensive bronchopneumonia in the lungs, and material was found in the larynx, trachea and bronchi that was apparently identical with the mixture that was being used for the tube feeding; however, no fat droplets, vegetable cells or other foreign bodies were present in the smaller bronchioles or in the alveoli. I am inclined to ascribe the pneumonia to aspiration of the tube feeding.

Dr. Franz T. Lipmann: I would like to ask how much confidence we may have in the sulfonamide determination. In the uremic patient there may be other substances in the blood that might react in the same way. The reaction for the sulfonamide might not be specific. I wonder if the sulfonamides were really still present in the blood?

Dr. Leaf: The same problem bothered us. I cannot give a definite answer. We did take blood from another patient who had uremia and a nonprotein nitrogen over 200 mg. per 100 cc.; it did not show any evidence of acetylated sulfonamides. I spoke to Dr. John Merrill at the Peter Bent Brigham Hospital about that point. He has seen a number of patients with lower-nephron nephrosis with marked retention of nonprotein nitrogen who had no evidence of "sulfa" drug in the blood. Hence it does not appear to be an invariable finding in the serum of patients with acute renal insufficiency, and therefore the likelihood of its having significance in this patient is increased.

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"ONE THING IS SURE"

"One thing is sure. Unless the doctors make their position clear some legislation might be engineered by lay groups, which not having the doctors' point of view, might do them a disservice." This telling sentence is from a communication by Dr. Robert C. Page, director of an important industrial health service and chairman of the National Doctors' Committee for Improved Federal Medical Services, an affiliate of the Citizens Committee for the Hoover Report. The committee's plea is that physicians inform themselves of the confused, duplicating situation in the Federal health services, reach conclusions about what should be done to correct the situation and make their suggestions available to Congress.

The Hoover Commission found five major and thirty smaller Federal medical systems with no central authority. Each system competes for appropriations and for scarce manpower and tries to build up its own chain of hospitals, without full consideration of the total picture and without regard for the existence of non-Federal hospitals.

Various proposals for improving the situation have produced cries from pressure groups, who thought that their toes were being trodden on, but little evidence of a statesmanlike approach to the problem. The Hoover Commission's recommendation that the major Federal health services be combined in a single agency may not be the best answer. Certainly it is not the only one that might reasonably be expected to produce economies and greater efficiency.

The important point stressed by Dr. Page's committee is that the Federal health services are important to all of us. It is our duty to make our voices heard — once we are sufficiently informed to know the tune we want to sing.

Committee on Medical Services, Commission on Organization of the Executive Branch of the Government. Medical Activities: Report to Congress. 57 pp. Washington, D. C.: United States Government Printing Office.

Leavell, H. R. National Health Service — recommendations of Hoover Commission. *New Eng. J. Med.* **241**:511-514, 1941.

Bills before 82nd Congress — S. 1140 and H. R. 3305 and 3688.

POSTGRADUATE MEDICAL CONFERENCE

The program of the second annual Western Massachusetts Postgraduate Medical Conference appears elsewhere in this issue of the *Journal*. The conference will be held again at the University of Massachusetts in Amherst; it is under the sponsorship of the Committee on Postgraduate Medical Education of the Massachusetts Medical Society in co-operation with the Hampden, Berkshire, Hampshire and Franklin district medical societies. A study of the program will disclose its scope and reveal the care that has gone into its preparation.

Postgraduate education in one form or another has always been a major function of medical societies. The Massachusetts Medical Society, increasingly aware of the importance of this function, has put increasingly greater efforts into it in recent years. The conference at Amherst is a result of the esteem in which both Mahomet and the mountain are held.

PINANSKI MEMORIAL FUND

THE late Judge Abraham E. Pinanski was not only an eminent jurist and philanthropist: he had in addition "a most affectionate and earnest concern" for the younger members of both his own and the medical profession. Such men may die, but they do not first grow old.

This interest in the younger man as well as in the relations between the professions was, in fact, so characteristic of Judge Pinanski that when Mrs. Pinanski was consulted in regard to a fitting memorial to her husband she suggested a series of annual lectures on the medical and legal aspects of the trial of cases.

The establishment of such a memorial has been set on foot, and already an impressive start has been made through a committee headed by Mr. Ralph Lowell, president of the Boston Safe Deposit and Trust Company, in raising a fund for the purpose. All money contributed to the memorial

> will be used to provide a series of such annual lectures and other lectures closely related thereto at law schools or medical schools, bar or medical associations under the direction of a lecture committee, consisting of four physicians, four lawyers and the President of the Boston Safe Deposit and Trust Company.

Such a monument serves better than stone to project into the future some of the virtue of the past.

LOCAL GIRL MAKES GOOD

MORE and more frequently the opportunity comes to acknowledge the deeds that women do publicly and to honor their doers. The occasion is naturally productive of more enthusiasm when the subject is one who is locally known and respected.

Dr. Martha May Eliot was mentioned in these columns in the fall of 1947, on the occasion of her election as the first woman president of the seventy-four-year-old American Public Health Association; she had at that time been associate chief of the Children's Bureau since 1941 and was shortly to become assistant director general of the World Health Organization, a post that she has held during the past two years.

In the four years since she was featured in these particular and somewhat exclusive columns she has also been president of the National Conference of Social Work, in 1949 and 1950, and has received the honorary degree of Doctor of Humane Letters from the University of Rochester in 1948 and that of Doctor of Science from Smith College in 1949.

Dr. Eliot's career, however, has definitely been linked with the Children's Bureau. Joining it as a staff member in 1924, she became assistant chief in 1934 and associate chief in 1941. Now, to climax this career, she is about to become its chief, on nomination of the President, to succeed Miss Katharine F. Lenroot, whose retirement has recently been announced.

Martha Eliot, a member of a Boston family known for its good works, was born in Dorchester on April 7, 1891. She was graduated from the Winsor School, and from Radcliffe College in 1913, after which she worked for a year in the Social Service Department of the Massachusetts General Hospital. She then entered Johns Hopkins University School of Medicine, where she graduated in 1918, going on to an internship at the Peter Bent Brigham Hospital.

As assistant and associate chief of the Bureau she was responsible for its health and medical services, and during World War II was author and director of the Emergency Maternal and Infant Care Program. In the World Health Organization she has been especially interested in the co-operative relations of the organization with the United Nations International Children's Emergency Fund.

Massachusetts has again the privilege of paying respect to a distinguished daughter!

Quite a new phase in the history of medicine is coming over this democratic country. Females are ambitious to dabble in medicine, as in other matters, with a view to reorganizing society.

Boston M. & S. J., *September 3, 1851*

MASSACHUSETTS MEDICAL SOCIETY

SECOND ANNUAL WESTERN MASSACHUSETTS POSTGRADUATE MEDICAL CONFERENCE

The second annual Western Massachusetts Postgraduate Medical Conference, sponsored by the Committee on Postgraduate Medical Education of the Massachusetts Medical Society, in co-operation with the Hampden, Berkshire, Hampshire and Franklin district medical societies will be held at the University of Massachusetts at Amherst on September 12 and 13.

WEDNESDAY MORNING, SEPTEMBER 12

First General Session

(Note: All sessions will be held in Stockbridge Hall.)

Chairman, Dr. Garvey Adeson, Pittsfield
Cochairman, Dr. Harwood W. Cummings, Greenfield

9:00 *Motion Pictures entitled "Primary Dysmenorrhea" and "Trichomonal and Monilial Vaginitis."*

10:00 *Symposium on Indigestion.* Dr. Franz J. Ingelfinger, Chairman. Associate professor of medicine, Boston University School of Medicine; visiting physician in medicine, Massachusetts Memorial Hospitals; chief of gastrointestinal clinic, Out-Patient Department, Massachusetts Memorial Hospitals; chief, gastrointestinal clinic, Cushing Veterans Administration Hospital, Framingham.

Dr. Francis D. Moore, Moseley Professor of Surgery, Harvard Medical School; surgeon-in-chief, Peter Bent Brigham Hospital.

Dr. W. Richard Ohler, formerly, assistant professor of medicine, Harvard Medical School; formerly, chief of Second Medical Service (Harvard), Boston City Hospital; president, Massachusetts Medical Society.

Dr. Robert E. Moss, instructor in psychiatry, Boston University School of Medicine; assistant in psychiatry, Massachusetts Memorial Hospitals; consultant to the Division of Student Health, Boston University.

Panel on Anesthesia

12:00 *Anesthesia for Poor-Risk Patients.* Dr. William Derrick, associate in anesthesia, Harvard Medical School; anesthetist, Peter Bent Brigham Hospital.

Anesthesia in Children. Dr. Robert M. Smith, chief anesthesiologist, Children's Medical Center; consultant in anesthesiology, Chelsea Naval Hospital.

Anesthesia in Obstetrics. Dr. Duncan E. Reid, professor of obstetrics, Harvard Medical School; chief of staff, Boston Lying-in Hospital.

Lunch (Greenough Cafeteria).

WEDNESDAY AFTERNOON, SEPTEMBER 12

Second General Session

Chairman, Dr. Lawrence N. Durgin, Amherst
Cochairman, Dr. Perrin N. Freeman, Greenfield

2:00 *Management of Burns.* Dr. Francis D. Moore, Moseley professor of surgery, Harvard Medical School; surgeon-in-chief, Peter Bent Brigham Hospital.

2:45 *Symposium on Obstetrics and Gynecology.* Dr. Duncan E. Reid, Chairman. Professor of obstetrics, Harvard Medical School; chief of staff, Boston Lying-in Hospital.

Dr. Howard Ulfelder, clinical associate in gynecology, Harvard Medical School; assistant surgeon, Massachusetts General Hospital.

4:20 *Motion Picture entitled "The Heart: Cardiovascular Pressure Pulses and Electrocardiography."*

WEDNESDAY EVENING, SEPTEMBER 12

6:00 Cocktail Hour (Rahar's Inn, Northampton).

7:00 Dinner (Rahar's Inn, Northampton).

Professor Curtis F. Canfield, professor of dramatics and director of the Kirby Memorial Theatre, Amherst College, will discuss "Inside Television."

Tickets for the dinner are $4.00, including tax and gratuity.

THURSDAY MORNING, SEPTEMBER 13

Third General Session

Chairman, Dr. Eric F. Joslin, Pittsfield
Cochairman, Dr. Allen G. Rice, Springfield

9:00 *A Motion Picture Entitled "The Heart: Electrokymography, Venous Catheterization and Angiocardiography."*

10:00 *Panel on Pulmonary Disease.* Dr. Donald S. King, Chairman. Courtesy staff, Massachusetts General Hospital.

Dr. Richard H. Overholt, clinical professor of surgery. Tufts College Medical School; thoracic surgeon, New England Deaconess Hospital.

Dr. Laurence L. Robbins, assistant professor of radiology, Harvard Medical School; radiologist-in-chief, Massachusetts General Hospital.

Dr. Theodore L. Badger, clinical associate in medicine, Harvard Medical School; visiting physician and chief of staff, Channing Home; consultant in diseases of the chest for Veterans Administration.

11:30 *Symposium on Heart Disease.* Dr. Louis Wolff, Chairman. Visiting physician and consultant to cardiac clinic, Beth Israel Hospital.

Dr. Robert S. Palmer, physician, Massachusetts General Hospital.

Dr. Laurence B. Ellis, assistant clinical professor of medicine, Harvard Medical School; chief, cardiology clinic, Boston City Hospital.

Lunch (Greenough Cafeteria).

THURSDAY AFTERNOON, SEPTEMBER 13

Fourth General Session

Chairman, Dr. James L. Smead, Springfield
Cochairman, Dr. Henry A. Tadgell, Belchertown

2:00 *Symposium on Back Pain.* Dr. Thomas B. Quigley, Chairman. Clinical associate in surgery, Harvard Medical School; senior associate in surgery, Peter Bent Brigham Hospital; surgeon, Harvard Athletic Association.

Management of Back Pain Caused by Abnormalities of Lower Back. Dr. Carter R. Rowe, assistant professor of orthopedic surgery, Harvard Medical School; assistant orthopedic surgeon, Massachusetts General Hospital; attending orthopedic surgeon, New England Peabody Home and Cushing Veterans Administration Hospital, Framingham.

Medical Aspects. Dr. Perry J. Culver, associate in medicine, Harvard Medical School; assistant physician, Massachusetts General Hospital.

Psychiatric Aspects. Dr. Nicholas Rizzo, instructor in psychiatry, Harvard Medical School; junior associate in psychiatry, Peter Bent Brigham Hospital.

Back Pain in Industry. Dr. H. Kelvin Magill, instructor in orthopedic surgery, Tufts College Medical School; assistant visiting surgeon, Boston City Hospital.

4:00 *Motion Pictures Entitled "Use of Artificial Kidney" and "Fractures: An Introduction."*

Emergency Telephone Service

Physicians will be located for emergency calls through the University of Massachusetts switchboard. The number is Amherst 900.

BOSTON MEDICAL LIBRARY

George Cheyne Portrait

The Library has recently received a fine copy of the mezzotint engraving of George Cheyne (1673–1743) by John Faber the younger. Taken from a painting of Cheyne by Johan Van Diest, a Dutch portrait painter living in London in 1732, Cheyne's age is given as 59. The portrait, if in existence, has not been located. Other copies of the engraving are recorded in the Bodleian Library, the Ashmolean Museum, Oxford, the British Museum and the Wellcome Historical Medical Museum, London. No copy was located in America in 1949 by Viets (George Cheyne, 1673-1743, *Bull. Hist. Med.* **23**: 435-452, 1949).

John Symcotts

Many documents in manuscript, including a case-book, a receipt book, medical notes, letters, wills and others, relating to John Symcotts, M.D. (1592?–1662), a Bedfordshire practitioner, who attended Oliver Cromwell, have survived. There are few similar records in existence, and no comparable collection has been published. The most important of these papers are now issued by the Bedfordshire Historical Record Society (1950) in a book competently edited by F. N. L. Poynter, with an introduction by W. J. Bishop, both of the Wellcome Historical Medical Library. In spite of the facts that this seventeenth-century physician had no stethoscope, no x-rays and no thermometer and that surgical intervention was in most cases precluded because there was no anesthesia and no antisepsis, Symcotts may be regarded as a skilled and experienced physician according to the standards of his time. Bishop finds him shrewd, patient, humane and resourceful. In his professional ethics, he lived up to the high standards of the medical profession.

Edward Jenner

The long anticipated *Bio-bibliography of Edward Jenner, 1749-1823*, by W. R. LeFanu, the distinguished librarian of the Royal College of Surgeons, has been published by Harvey and Blythe, London, 1951, in a limited edition of one thousand numbered copies. Each book and paper by Jenner is fully described, including the three editions of the cow-pox *Inquiry;* in addition, there is a long section devoted to Jenner's correspondence. The index of recorded copies of books and letters appears to be full. The Library is credited with thirteen items, including the first and second editions of the *Inquiry* (1798 and 1800). Missing are the third edition (1801) and the uncommon American imprint, Springfield, Illinois (1802). The Library does, however, have *Further Observations* (1799) and the rare American leaflet of instructions (1802). The last was printed from a letter to Benjamin Waterhouse. The frontispiece of LeFanu's book is a reproduction of the superb pastel of Jenner, by John Raphael Smith, now in the Wellcome Museum.

Naparsimasonut Ikiortiksat

Publication has been arranged for a reprinting of this book, the first medical work issued in Greenland (1856). The Library acquired a copy in 1939, only one other being recorded in America, at Stanford University Library. The booklet of sixteen pages gives instructions on remedies for the sick by the inspector and physician of Godthaab. It is written in the Eskimo language. Danish and English translations will be included in the new printing, to be carried out in Copenhagen for the librarian, in addition to the original text in Eskimo.

During the summer of 1950, Charles C. Colby, III, reference librarian of the Boston Medical Library, made a trip to Germany to study medical libraries and collections in Western Germany. A report of his investigations was issued by the State Department in a limited edition on October 13, 1950.

NEW HAMPSHIRE MEDICAL SOCIETY

OBITUARY

DR. LOUIS B. MARCOU

Dr. Louis B. Marcou, prominent local physician and surgeon, died on June 15 at the St. Louis Hospital in Berlin.

Dr. Marcou was born March 13, 1874, in Benton, Maine, the son of Joseph and Mary Roderick Marcou, and attended school in Fairfield, Maine. After becoming a registered pharmacist he attended

Boston University and the University of Vermont Medical School, graduating in 1899. He did graduate work in Austria and Germany in 1903 and later studied surgery in Paris in 1921.

Dr. Marcou had been on the staff of the St. Louis Hospital since its opening in 1905, having been active president of the medical staff for twenty-five years.

He served as a captain in the Medical Corps during World War I and received the President's Medal as Selective Service examiner during World War II.

Dr. Marcou belonged to the Coos County, State Medical and American Medical associations and was a fellow of the American College of Surgeons. He organized the Cancer Clinic in Berlin, was the first president of the Rotary Club and a member of the American Legion and Elks Club and served on the board of directors of the Berlin Savings Bank and Trust Company and on the Board of Education. He was chairman of the Board of Health and an honorary member of the Apalaches Club of Rimouski, Province of Quebec.

His first wife, Laura Parent Marcou, died in 1927. In 1929 he married Yvonne Chrétien, who survives him. He also leaves two daughters, Miss Lois-Joan Marcou and Miss Claudia Marcou of Berlin; two sisters, Mrs. Beatrice Garneau of Portland, Maine, and Mrs. Cora Bailey of Northboro, Massachusetts; one brother, Arthur, of Brookline, Massachusetts; and several nieces and nephews.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JULY, 1951

RÉSUMÉ

Disease	July 1951	July 1950	Seven-Year Median
Chancroid	1	1	2
Chicken pox	438	475	516
Diphtheria	3	6	14
Dog bite	1382	1475	1316
Dysentery, bacillary	10	9	9
German measles	202	114	47
Gonorrhea	214	186	352
Granuloma inguinale	1	0	0
Lymphogranuloma venereum	0	0	0
Malaria	20	1	15
Measles	1202	1162	876
Meningitis, meningococcal	3	1	5
Meningitis, Pfeiffer-bacillus	2	2	2
Meningitis, pneumococcal	0	2	2
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	1	0
Meningitis, undetermined	12	4	3
Mumps	784	383	434
Poliomyelitis	69	19	21
Salmonellosis	7	1	8
Scarlet fever	120	125	179
Syphilis	139	75	225
Tuberculosis, pulmonary	194	198	243
Tuberculosis, other forms	20	13	13
Typhoid fever	3	3	3
Undulant fever	0	3	4
Whooping cough	111	432	432

COMMENT

The diseases notably above the seven-year median for July are German measles, malaria, measles, mumps and poliomyelitis.

Diseases below the seven-year median for the month are chicken pox, diphtheria, scarlet fever, undulant fever and whooping cough.

The 3 cases of diphtheria reported for July are the lowest incidence of this disease for any month in our records.

The number of cases of mumps is the second highest ever reported for the month of July in Massachusetts.

The 69 cases of poliomyelitis represent a higher incidence for the month than that of last year; however, it is considerably below the 1949 figure of 91 cases for July.

One hundred and twenty cases of scarlet fever is the second lowest incidence of this disease ever reported for this month.

This is the first July since 1934 that no cases of undulant fever have been reported in the State.

One hundred and eleven cases of whooping cough is the second lowest incidence of the disease noted for any month in our records.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from: Cambridge, 1; Revere, 2; total, 3.

Dysentery, bacillary, was reported from: Belchertown, 4; Cambridge, 6; total, 10.

Encephalitis, infectious, was reported from: Marlboro, 1; Pittsfield, 1; Southbridge, 1; total, 3.

Hepatitis, infectious, was reported from: Haverhill, 1; Sturbridge, 5; total, 6.

Malaria was reported from: Murphy Army Hospital, 20; total, 20.

Meningitis, meningococcal, was reported from: Gloucester, 1; New Bedford, 1; Waltham, 1; total, 3.

Meningitis, Pfeiffer-bacillus, was reported from: Holyoke, 1; South Hadley, 1; total, 2.

Meningitis, mumps, was reported from: Norwood, 1; total, 1.

Meningitis, undetermined, was reported from: Arlington, 1; Cambridge, 1; Greenfield, 1; Lynn, 1; Newton, 1; Pittsfield, 1; Springfield, 3; Quincy, 2; Worcester, 1; total, 12.

Poliomyelitis was reported from: Adams, 1; Arlington, 1; Ashburnham, 1; Ashby, 1; Beverly, 1; Boston, 4; Brewster, 1; Brockton, 1; Brookline, 1; Cambridge, 2; Fitchburg, 1; Framingham, 2; Gloucester, 1; Greenfield, 3; Hamilton, 1; Holyoke, 1; Lexington, 1; Lowell, 1; Lynn, 2; Manchester, 1; Marlboro, 11; Medford, 1; Natick, 1; Northfield, 5; Norwood, 1; Oxford, 1; Plymouth, 1; Randolph, 2; Revere, 1; Salem, 1; Saugus, 1; Sherborn, 1; Somerville, 4; South Hadley, 1; Springfield, 1; Stoneham, 1; Wareham, 2; Watertown, 1; Weston, 1; Wilmington, 2; Worcester, 1; total, 69.

Salmonellosis was reported from: Boston, 1; Danvers, 3; Monterey, 1; Wilbraham, 1; Woburn, 1; total, 7.

Septic sore throat was reported from: Adams, 2; Boston, 2; Lynn, 2; total, 6.

Typhoid fever was reported from: Greenfield, 1; Revere, 1; Winthrop, 1; total, 3.

BOOK REVIEWS

Sir Thomas Browne: A doctor's life of science and faith. By Jeremiah S. Finch, assistant dean of the college, Princeton University. 8°, cloth, 319 pp., with 18 illustrations. New York: Henry Schuman, Incorporated, 1950. $3.00.

Sir Thomas Browne is one of the first and choicest of the master spirits of all ages, who, distinguished in science, have been even more distinguished in the fields of literature, and his inspired *Religio Medici* is the heart and soul of his religious and scientific faith. The author of the present urbane and scholarly biography, himself a distinguished man of letters from the Princeton faculty, has aptly made it the keynote and point of departure for his study of the doctor's life. His factual account of Sir Thomas Browne's career and its Elizabethan background is in itself a fascinating story, but still more revealing and sympathetic is his literary and spiritual appraisal of the significance of the *Religio Medici*.

As a confession of personal faith and scientific creed, the *Religio Medici* has appealed particularly to physicians in every succeeding age, to Sir William Osler and to our own Harvey Cushing, who exemplified its teaching in his life and works, and on it patterned his own memorable *Consecratio Medici*.

Sir Thomas Browne was a man whose life was cast in the pathways of science but whose spirit dwelt always in the glory and revealing light of the arts. It was a sacrificing but triumphant life of devotion and service both to religion and to science. Like his great contemporary, Sir Thomas More, he was humanist become hero. ROBERT M. GREEN, M.D.

The Neurologic Examination: Incorporating the fundamentals of neuroanatomy and neurophysiology. By Russell N. DeJong, M.D. 4°, cloth, 1079 pp., with 299 illustrations. New York: Paul B. Hoeber, Incorporated, 1950. $15.00.

This volume of over 1000 pages is an exhaustive treatise on neurologic examination, with every aspect competently set forth and with excellent illustrations and references to the literature. The only criticism would be that in developing such a large treatise the author has cut off neurology from the rest of medicine, tending to make it a separate entity. The book is too big and too expensive for the average medical student, who could most profit by its use. To the neurologist and the neurosurgeon, it should be of considerable value as a reference text. To the others, its bulk and cost set up a barrier against the wide distribution that the book so richly deserves.

HENRY R. VIETS, M.D.

NOTICES

ANNOUNCEMENTS

Drs. P. F. Butler and C. W. Blackett announce that Dr. Howard L. Leary has become associated with them in the practice of radiology at 35 Bay State Road, Boston.

Dr. Iver S. Ravin announces the opening of his office for the practice of internal medicine at 371 Commonwealth Avenue, Boston.

Dr. Eugene Suzedell announces the opening of his office for the practice of orthopedic surgery at 59 Coddington Street, Quincy.

NATIONAL GASTROENTEROLOGICAL ASSOCIATION

The National Gastroenterological Association will hold its sixteenth Annual Convention and Scientific Sessions at the Hotel Drake in Chicago, Illinois, on September 17, 18 and 19. Further information concerning the program and details of the course may be obtained by writing to the Secretary, National Gastroenterological Association, 1819 Broadway, New York 23, N. Y.

SPRINGFIELD ACADEMY OF MEDICINE

A meeting of the Springfield Academy of Medicine will be held in the Woman's Club Building, 43 Spring Street, on October 9 at 8:30 p.m. A symposium on the Medical Aspects of Atomic Warfare, under the direct sponsorship of Yale University School of Medicine, will be presented.

EASTERN SECTION, AMERICAN TRUDEAU SOCIETY

The annual meeting of the Eastern Section of the American Trudeau Society will be held Friday and Saturday, November 2 and 3, at Hartford, Connecticut, with headquarters at the Hotel Bond. Members of the society who wish to present papers are urged to communicate promptly with the chairman of the program committee, Dr. Kirby Howlett, Laurel Heights Sanatorium, Shelton, Connecticut.

MASSACHUSETTS HEART ASSOCIATION

The American Heart Association has issued the first revision of its manual for physicians, "Examination of the Heart," originally published in 1940. The initial limited printing is being made available free to physicians concerned with the diagnosis of cardiovascular diseases. Requests for the booklet should be directed to the Massachusetts Heart Association, 650 Beacon Street, Boston 15.

ESSAY AWARD

The Board of Regents of the American College of Chest Physicians offers a cash prize award of $250, to be given annually for the best original contribution, preferably by a young investigator, on any subject relating to chest disease.

Further information may be obtained from the Executive Office, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The annual meeting of the American Board of Obstetrics and Gynecology was held in New York City May 10-16, at which time 248 candidates were certified.

New bulletins, incorporating changes made at the recent meeting, will be available for distribution shortly. These changes include adoption of the following:

Effective January 1, 1952, case reports from one's residency service shall not be more than 5 in number. Exchange residencies into other specialties cannot be subtracted from the minimal required three years of training divided between obstetrics and gynecology. Application for re-examination in Part II must be made by the candidate prior to February 1 of any year. A blank logbook entitled "Medical Officer's Professional Training Record" is obtainable from the Offices of the Surgeons General. This record should be carefully kept and attested to while in military service.

The next scheduled examination (Part I), — written examination and review of case histories, — for all candidates will be held in various cities of the United States and Canada on Friday, February 1, 1952. Application for examination or re-examination must be made by the candidate prior to November 1, 1951.

Concerning limited or unilateral certification: This board has always required training in both branches (obstetrics and gynecology) for all candidates. For the first ten years of the board's activities this rule was not rigidly enforced, and many men trained and practicing in only one branch were granted the Board's regular joint certification if they could demonstrate a fundamental knowledge of the other branch. Since 1940 evidence of adequate training in both branches has been rigidly required, and bilateral training is now an accepted essential in all approved residency or other training programs leading toward certification in obstetrics and gynecology. For the benefit of those trained before this became universal practice (namely, prior to January 1, 1939), the board has now arranged to accept for examination and unilateral certification in obstetrics or in gynecology men who have been or otherwise would be declared ineligible for lack of training in both branches.

Complete information regarding requirements and other details of limited certification is to be found in the 1951 Bulletin of this Board.

Application forms and bulletins are sent upon request made to: Robert L. Faulkner, M.D., Secretary, American Board of Obstetrics and Gynecology, 2105 Adelbert Road, Cleveland 6, Ohio.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 11. Springfield Academy of Medicine. Page 274, issue of August 16.

SEPTEMBER 11–13. Clinical Congress. Page 158, issue of July 26.

SEPTEMBER 12–14. Biological Photographic Association, Inc. Annual Meeting, Boston.

SEPTEMBER 17–19. National Gastroenterological Association. Notice above.

SEPTEMBER 19. American Medical Writers' Association. Page 1066, issue of December 28.

SEPTEMBER 19–21. Mississippi Valley Medical Society. Page 1066, issue of December 28.

SEPTEMBER 30–OCTOBER 2. New Hampshire Medical Society. Annual Meeting. Equinox House, Manchester, Vermont.

OCTOBER 9. Springfield Academy of Medicine. Notice above.

OCTOBER 22–24. American Association of Blood Banks. Page 316, issue of August 23.

OCTOBER 22–27. Medico-Military Symposium. Page 234, issue of August 9.

OCTOBER 29. New York Institute of Clinical Oral Pathology. Page xv, issue of June 14.

OCTOBER 29–NOVEMBER 2. American Public Health Association. Page 316, issue of August 23.

OCTOBER 31. New England Obstetrical and Gynecological Society, Hotel Somerset, Boston.

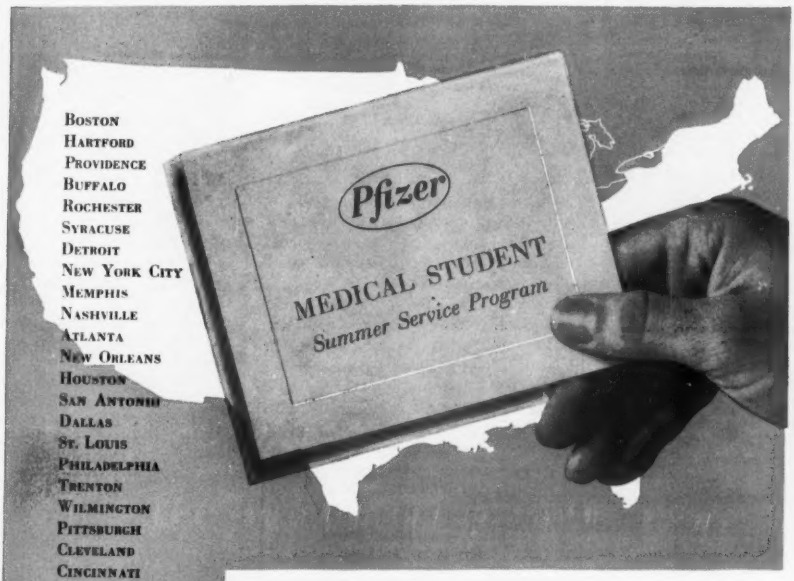
NOVEMBER 2 AND 3. Eastern Section, American Trudeau Society. Notice above.

NOVEMBER 4 AND 5. American Society for the Study of Arteriosclerosis. Page xv, issue of July 12.

NOVEMBER 7–19. Pan-Pacific Surgical Association. Page 820, issue of May 24.

DECEMBER 11–19. International Congress on Mental Health. Page xiii, issue of July 26.

(*Notices concluded on page xiii*)



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A PIONEER group of 70 medical students, 3rd and 4th year leaders from some of the nation's outstanding medical schools, have been selected for a special course in antibiotics covering recent research and clinical developments. These young men and women are qualified to serve physicians in 36 major cities during their summer vacation and will make available reprints, abstracts, bibliographic research and other data as requested by members of the profession.

At the same time they have the invaluable opportunity of acquainting themselves with current clinical practices of leading general practitioners, specialists, teaching institutions and other professional groups.

This new Pfizer activity will supplement other Pfizer services such as the Antibiotics Newsletter, now being prepared and distributed semi-monthly by the Medical Service Department.

ANTIBIOTIC DIVISION Pfizer CHAS. PFIZER & CO., INC., *Brooklyn 6, New York*

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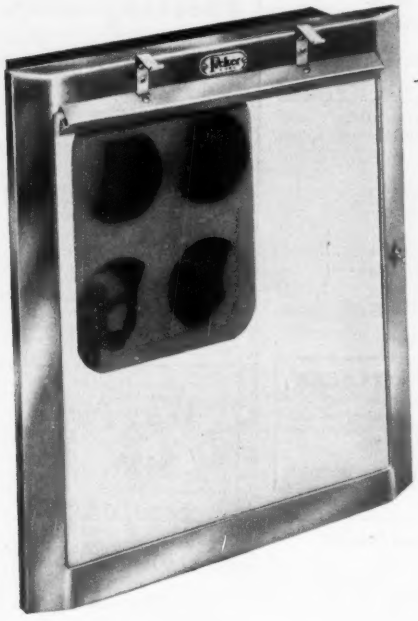

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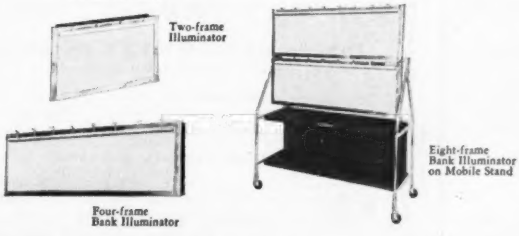

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NOTICES (*Concluded from page 350*)

DECEMBER 14 AND 15. Association for Research in Nervous and Mental Disease. Page 958, issue of June 21.

JULY 8–11, 1952. Thirteenth British Congress of Obstetrics and Gynaecology. Page xv, issue of December 14.

JULY 14–19, 1952. International Congress of Physical Medicine. Page 998, issue of June 28.

DISTRICT MEDICAL SOCIETY

HAMPSHIRE

NOVEMBER 7. Northampton State Hospital, Northampton.
JANUARY 2. Veterans Hospital, Northampton.
MARCH 5. Cooley-Dickinson Hospital, Northampton.
MAY 7. Annual Meeting. Jones Library, Amherst.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 6

THURSDAY, SEPTEMBER 6

*9:00–10:00 a.m. Grand rounds. Robert Breck Brigham Hospital.
*9:00–10.00 a.m. Cardiac grand rounds. Main Amphitheater, Children's Medical Center.

FRIDAY, SEPTEMBER 7

*9:00 a.m.–12:00 m. Combined medical and surgical staff rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical clinic. South End Health Unit, 57 East Concord Street, Boston.
*1:30 p.m. Tumor clinic. Outpatient Department, Mount Auburn Hospital, Cambridge.

MONDAY, SEPTEMBER 10

*11:30 a.m.–12:15 p.m. Clinical conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.
*12:15–1:15 p.m. Clinicopathological conference. Main Amphitheater, Peter Bent Brigham Hospital.

TUESDAY, SEPTEMBER 11

*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.
*1:30–2:30 p.m. Pediatric rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

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PEDIATRICS, October 22–November 3, 1951

General clinical pediatrics taught on the wards of the Boston Floating Hospital under the direction of Dr. Irving Silverman in association with staff members and guest lecturers. The faculty will include Drs. J. M. Baty, M. L. Brodny, E. A. Brown, M. Cohen, R. Freeman, M. Kriedberg, F. McDonald, E. Place, R. Wagner and Priscilla White. Topics will include GU conditions, allergy, dental problems, emotional problems, antibiotics, contagious diseases, endocrinology, diseases of the blood, surgery, kidney diseases, and diabetes. Enrollment limited to 15. Tuition fee — $75.

PROCTOLOGY I, October 22-26, 1951

Illustrated lectures on bleeding per ano, hemorrhoids, cryptitis, fissures, abscesses, fistulas, pruritus ani, constipation, tumors, prolapse, strictures, the colitises, diverticulitis, x-ray diagnosis, etc. Observation of operations in the rectal clinics of the Boston Dispensary and the Mt. Auburn Hospital. Dr. Edward T. Whitney in charge. Enrollment limited to 12. Tuition fee — $40.

DERMATOLOGY I, November 5-9, 1951

Diagnosis and treatment of the more common skin diseases and syphilis. Methods for detecting and identifying fungi, laboratory procedures in mycology, physical therapy (with outlines on the use of x-ray and radium), and topical therapy. Clinic demonstrations. Dr. Francis M. Thurmon in charge. Enrollment limited to 20. Tuition fee — $40.

NEURO-OPHTHALMOLOGY, November 26-30, 1951

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